STUDIES ON THE REACTIONS OF CHLOROSULPHONYL ISOCYANATE, SULPHURYL CHLORIDE, CERIC AMMONIUM NITRATE and PHOTOCHEMISTRY OF SOME CHALCONES

By

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INDIAN INSTITUTE OF TECHNOLOGY KANPUR

JUNE, 1985

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A Thesis Submitted
in Partial Fulfilment of the Requirements
for the Degree of
DOCTOR OF PHILOSOPHY

By
SUDHA RANI GUPTA

to the

DEPARTMENT OF CHEMISTRY
INDIAN INSTITUTE OF TECHNOLOGY KANPUR
JUNE, 1985

When the earth is enveloped in darkness, it is the sun's rays of light which gradually dissolve the mystery, illuminate it and allow it to unfold and reveal its true beauty and majesty in full splendour. Likewise the darkness of ignorance is dispelled only by the guidance and knowledge of the SUPREME ONE.

MY SALUTATIONS TO HIM

To

My Inspiration

STATEMENT

I hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology, Kanpur, India, under the supervision of Professor Durga Nath Dhar.

In keeping with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigators.

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CERTIFICATE I

This is to certify that Miss Sudha Rani Gupta has satisfactorily completed the following courses required for the Ph.D. degree programme.

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Certified that the work embodied in this thesis entitled: 'STUDIES ON THE REACTIONS OF CHLOROSULPHONYL ISOCYANATE, SULPHURYL CHLORIDE, CERIC AMMONIUM NITRATE AND PHOTOCHEMISTRY OF SOME CHALCONES' has been carried by Miss Sudha Rani Gupta under my supervision and the same has not been submitted elsewhere for a degree.

D N Dhar

Durga Nath Dhar
Thesis Supervisor

Kanpur
June 1985.

ACKNOWLEDGEMENTS

It is with a profound sense of gratitude that I wish to thank Professor Durga Nath Dhar whose constant guidance has not only enhanced the technical merit of this work but has also ensured the completion of this otherwise impossible task.

I wish to express my sincere thanks to Drs. Y.D. Vankar and S. Chandrasekaran for invaluable discussions and all other help rendered to me.

I extend my whole hearted appreciation to my colleagues, Dr. K.S. Keshavamurthy, Dr. A.K. Bag, Dr. Sunita Joshi, Dr. Uma K. Tiwari, Messers Sajan P. Joseph, E. Sampath Kumar, Manisha Tripathi and Chandra Bhattacharjee and all others working in the core lab, whose ideas and comments are incorporated in this thesis.

My thanks are due to the chemistry technical staff, (stores, workshop), and the institute glass blowing services for the generous help.

I would like to express my appreciation to Drs. and Mesdames Chandrasekaran, Dhar, Gupta, Rama, Theraja, Vankar for providing me a homely atmosphere.

My thanks are due to Mr. R.K. Rajpal, (for drawings), Mr. Anil Johri (typing) and Mr. B.S. Shukla (cyclostyling) and for other help extended to me.

I am grateful to Mr. and Mrs. V.K. Jayaswal, Mr. and Mrs. R.A. Agrawal for their affectionate encouragement. My words fail to thank Anita, Aprana and Rajandraji for instilling in me the feeling of belonging to them.

It is beyond my words to thank the members of my family for the opportunity they have provided me, and for the love and affection bestowed on me.

Sudha

PREFACE

The thesis has been divided into four chapters. Chapter I describes the reaction of versatile uniparticulate electrophile, the chlorosulphonyl isocyanate (CSI) towards pyrazoles, 2-pyrazolin-5-ones, 1,2,3,4-tetrahydrocarbazoles and isoxazoles. We have studied the reaction of CSI with pyrazole, 3,5-dimethylpyrazole, 3-metnyl-5-ethoxypyrazole, 1-[4-nitrophenyl]-3-methyl-5-ethoxy pyrazole, 1-[2,4-dinitrophenyl]-3,5-dimethyl-pyrazole, 1-[2,4-dinitrophenyl]-3-methyl-5-phenyl-pyrazole, 1-[4-nitrophenyl]-3,5-dimethyl pyrazole, 1-phenyl-3-methyl-5-hydroxy-pyrazole, 1-[4-nitrophenyl]-3-methyl-5-hydroxy-pyrazole, 1-[2,4-dinitrophenyl]-3-methyl-5-hydroxy-pyrazole.

2-pyrazolin-5-ones, 1,2,3,4-tetrahydrocarbazoles and isoxazoles taken for the present study include, 1-[4-nitrophenyl]-3-methyl-2-pyrazolin-5-one, 1-[2,4-dinitrophenyl]-3-methyl-2-pyrazolin-5-one, 6,8-dinitro-1,2,3,4-tetrahydrocarbazole, 6-nitro-1,2,3,4-tetrahydrocarbazole, 3,5-dimetnyl-isoxazole, and 4-phenyl-3-methyl-5-amino-isoxazole.

Reaction of 3,5-dimethyl-pyrazole, 3-methyl-5-ethoxy-pyrazole with CSI took place smoothly producing intermediates, 3,5-dimethyl-pyrazol-1-N-chlorosulphonyl-carboximide, 3-methyl-5-ethoxy-pyrazol-1-N-chlorosulphonyl-carboximide respectively. The later compound on alkaline hydrolysis yielded 3-methyl-5-ethoxy-pyrazol-1-N-carboximide. Reaction of pyrazole with CSI, produced pyrazol-1-N-sulphonamide.

Reaction of 3,5-dimethyl-pyrazole with CSI also afforded 3,5-dimethyl-1-N-sulphonamide. The reaction of 1-[4-nitrophenyl]-3-methyl-5-ethoxy-pyrazole with CSI for 0.5 hr, produced 1-[4-nitrophenyl]-3-methyl-5-ethoxy-pyrazol-4-chlorosulphonyl-carboximide. The latter compound on alkaline hydrolysis afforded 1-[4-nitrophenyl]-3-methyl-5-ethoxy-pyrazol-4-carboximide. Treatment of 1-[4-nitrophenyl]-3-methyl-5-ethoxy-pyrazol-4-chlorosulphonyl-carboximide with DMF furnished the corresponding carbonitrile.

The reaction of 2-pyrazolin-5-ones on treatment with CSI produced the corresponding 2-pyrazolin-5-imide. Here the (2+2) cycloaddition takes place at the C=O group of the 2-pyrazolin-5-one. 6,8-Dinitro-1,2,3,4-tetrahydrocarbazole and 6-nitro-1,2,3,4-tetrahydrocarbazole on treatment with CSI yielded 6,8-dinitro-1,2,3,4-tetrahydrocarbazole-N-chlorosulphonyl-carboximide and 6-nitro-1,2,3,4-tetrahydrocarbazole-N-chlorosulphonyl-carboximide, respectively. The latter compound on hydrolysis yielded the corresponding N-carboximide.

3,5-dimethyl-isoxazole, 4-phenyl-3-methyl-5-amino-isoxazole on treatment with CSI gave rise to 3,5-dimethyl-isoxazol-4-sulphonamide and 5-[4-phenyl-3-methyl]-isoxazolyl-urea respectively.

The Chapter II deals with the modified Ritter reaction of sulphuryl chloride with various Schiff's bases in acetonitrile, benzonitrile, dimethyl sulphoxide and ethyl cyanoacetate respectively. Reaction of the following Schiff's bases with sulphuryl chloride (1:1), in acetonitrile have been studied.

N-[p-bromobenzylidene]-aniline(78a), N-[p-chlorobenzylidene]-p-chloro-aniline (78b), N-[benzylidene]-aniline (78c), N-[p-chloro-benzylidene]aniline (78d), N-[benzylidene]-p-chloro-aniline (78e), N-[benzylidene]-p-nitro-aniline (78f), N-[p-nitrobenzylidene]-p-nitro-aniline (78g), N-[p-nitrobenzylidene]-m-nitro-aniline (78h), N-[p-nitrobenzylidene]-o-nitroaniline (78i), N-[benzylidene]-m-nitro-aniline (78j), N-[benzylidene]-o-nitro-aniline (78k), n-[p-bromobenzylidene]-p-nitro-aniline (78l), N-[3,4-dimethoxy benzylidene]-m-nitro-aniline (78m), N-[3,4-dimethoxy-benzylidene]-aniline (78n), N-[3,4-dimethoxy-benzylidene]-p-chloro-aniline (78o), N-[p-methoxy-benzylidene]-aniline (78p), N-[p-methoxy-benzylidene]-p-chloro-aniline (78q), N-[3,4-dimethoxy-benzylidene]-p-methoxy-aniline (78r) and aldazines (97a-f).

The above modified Ritter reaction was studied with the following Schiff's bases, in the presence of SO_2Cl_2-DMSO. N-[3,4-dimethoxy-benzylidene]-aniline, N-[p-methoxy-benzylidene]-aniline, N-[p-methoxy-benzylidene]-p-chloro-aniline, N-[3,4-dimethoxy-benzylidene]-p-methoxy-aniline. An analogous study has been made, involving the reaction of sulphuryl chloride-ethyl cyanoacetate with some of the Schiff's bases (vide infra), N-[benzylidene]-p-chloro-aniline, N-[benzylidene]-p-nitro-aniline, N-[benzylidene]-m-nitro-aniline, and N-[p-nitrobenzylidene]-m-nitro-aniline.

Likewise, the interaction of SO_2Cl_2-C_6H_5CN with the following Schiff's bases has been investigated. N-[benzylidene]-aniline,

N-[p-chlorobenzylidene]-p-chloro-aniline, N-[p-chloro-benzylidene]-aniline. The reaction of Schiff's bases (78d-m) with sulphuryl chloride in acetonitrile took place smoothly giving rise to the corresponding N-phenyl-benzimidines (85d-m) respectively. Treatment of Schiff's bases (78a-c) with sulphuryl chloride in acetonitrile produced benzaldehyde-phenyl-hydrazones. The latter compounds are formed via the diaziridine intermediates.

Reaction of Schiff's bases (78n-q) with sulphuryl chloride in acetonitrile furnished the corresponding benzanilides. The same products, viz., benzanilides (95o,p,q) were isolated, if acetonitrile is replaced by dimethylsulphoxide (DMSO) in the above reaction. However, in the reaction of N-[3,4-dimethoxybenzylidene]-aniline (78n) with SO_2Cl_2-DMSO, the oxaziridine derivative was formed.

Reaction of Schiff's bases (78d-g) with sulphuryl chloride in ethyl cyanoacetate also afforded the N-phenyl benzimidines. Aldazines (97a-f) on treatment with SO_2Cl_2-CH_3CN gave rise to the corresponding α-chloroaldazines. Reaction of N-[benzylidene]-p-chloro-aniline (78e) with sulphuryl chloride in ethyl cyanoacetate also yielded the benzimide chloride. Treatment of SO_2Cl_2-C_6H_5CN with N-[benzylidene]-aniline, N-[p-chloro-benzylidene]-aniline gave rise to their corresponding N-phenyl-benzimidines respectively. Reaction of N-[p-chloro-benzylidene]-p-chloro-aniline with SO_2Cl_2-C_6H_5CN produced the corresponding benzaldehyde-phenyl-hydrazone.

In Chapter III are described the ceric ammonium nitrate oxidation of some esters, aldazines and heterocycles. The esters, aldazines and heterocycles taken for the present study include methyl-benzoate, ethyl-benzoate, n-propyl-benzoate, ethyl-p-chloro benzoate, allyl-m-chloro-benzoate, allyl-p-toluate, allyl-p-methoxy benzoate, benzyl-benzoate, benzyl-p-chloro-benzoate, benzyl-p-toluate, ethyl-phenyl-acetate, n-propyl-phenyl-acetate, aldazines (139a-j), 1-phenyl-3-methyl-2-pyrazolin-5-one; 1-[4-nitrophenyl]-3-methyl-2-pyrazolin-5-one; 1,2,3,4-tetrahydro_carbazole, 1-[2,4-dinitro_phenyl]-3,5-dimethyl-pyrazole.

Oxidative cleavage of esters with CAN has been studied (in 1:4 molar ratio) at reflux temperature for 5-6 hr, resulting in the formation of their corresponding acids. The oxidative cleavage of aldazines has been effected by CAN in 1:6 molar ratios, in acetonitrile at reflux temperature for 1.5 hr, and giving rise to the corresponding aldehydes, which were characterized by the preparation of their 2,4-dinitro-phenyl-hydrazones. Treatment of ceric ammonium nitrate with some heterocycles (in 1:4 molar ratio), such as, 1-phenyl-3-methyl-2-pyrazolin-5-one, 1-[4-nitrophenyl]-3-methyl-2-pyrazolin-5-one; and 1,2,3,4-tetrahydrocarbazole took place smoothly producing their corresponding dimers viz., 4,4'-bis-1-phenyl-3-methyl-2-pyrazolin-5-one; 4,4'-bis-1-[4-nitro-phenyl]-3-methyl-2-pyrazolin-5-one; N,N'-bis-1,2,3,4-tetrahydrocarbazole respectively. 1-[2,4-dinitro-phenyl]-3,5-dimethyl-pyrazole on treatment with CAN produced a hitherto unreported heterocycle.

The Chapter IV deals with the study of the photochemical irradiation of some substituted chalcones, viz., 4'-chloro-chalcone, 3,4-dimethoxy-4'-chloro-chalcone, 4'-chloro-4-aceta-mido-chalcone. The photochemical irradiation of above chalcones has been carried out in different solvents such as benzene, acetone, methanol, ethanol, acetic acid, employing the molecular oxygen. Reactions were carried out using Srinivasan Griffin Rayonet photochemical reactor, equipped with 2537Å light source.

Irradiation of 4'-chloro-chalcones, 3,4-dimethoxy-4'-chloro-chalcone in acetone/molecular oxygen, for 46 hr, gave rise to their corresponding indenones.

4'-chloro-chalcone, 3,4-dimethoxy-4'-chloro-chalcone in benzene/molecular oxygen were photochemically irradiated for 44 hr, leading to the formation of flavanones. Irradiation of 4-chloro-chalcone (as well as 3,4-dimethoxy-4'-chloro-chalcone) in methanol-O_2, yielded p-chloro-benzoic acid.

CONTENTS

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CHAPTER-I

REACTIONS OF CHLOROSULPHONYL ISOCYANATE WITH PYRAZOLES, 2-PYRAZOLINE-5-ONES, ISOXAZOLES AND 1,2,3,4-TETRAHYDROCARBAZOLES

I.1 ABSTRACT

The reaction of the versatile uniparticulate electrophile (CSI) towards pyrazoles, 2-pyrazolin-5-ones, 1,2,3,4-tetrahydrocarbazoles and isoxazoles have been investigated. We have studied the reaction of CSI with pyrazole, 3,5-dimethyl-pyrazole, 3-methyl-5-ethoxy-pyrazole, 1-[4-Nitro-phenyl]-3-methyl-5-ethoxy-pyrazole, 1-[2-4-dinitro-phenyl]-3,5-dimethyl-pyrazole, 1-[2,4-dinitrophenyl]-3-methyl-5-phenyl-pyrazole, 1-[4-Nitro-phenyl]-3,5-dimethyl-pyrazole, 1-phenyl-3-methyl-5-hydroxy-pyrazole, 1-[4-Nitro-phenyl]-3-methyl-5-hydroxy-pyrazole, 1-[2,4-dinitro-phenyl]-3-methyl-5-hydroxy-pyrazole.

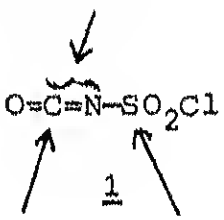
2-pyrazolin-5-ones, 1,2,3,4-tetrahydrocarbazoles and isoxazoles taken for the present study include, 1-[4-Nitro-phenyl]-3-methyl-2-pyrazolin-5-one, 1-[2,4-dinitro-phenyl]-3-methyl-2-pyrazolin-5-one, 6,8-dinitro-1,2,3,4-tetrahydro-carbazole, 6-Nitro-1,2,3,4-tetrahydrocarbazole, 3,5-dimethyl-isoxazole, 4-phenyl-3-methyl-5-amino-isoxazole,

In all the above cases the 1:1 adduct formation has been established on the basis of mass spectroscopic data.

1.2 INTRODUCTION

Chlorosulphonyl isocyanate (CSI) discovered by Graf[1,2] in 1952, is the most reactive isocyanate known. The polar chlorosulphonyl group attached to the cumulative double bond in CSI, enhances the reactivity of isocyanate group such that the carbon atom becomes strongly electrophilic.[3] This reagent has received considerable attention[4-7] owing to its reactivity as a uniparticulate electrophile and as a heterocumulene in cycloaddition reaction with multiple bonds.

If one conceives CSI as an electrophile, there are two sites of attack by nucleophilic species, viz., the sulphonyl and carbonyl groups. In addition, the cycloaddition to the C=N of cumulative function can also occur. CSI undergoes all these three types of reactions.



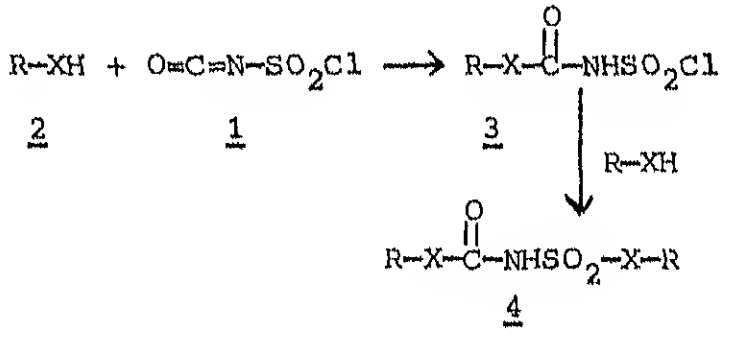
1

Reactions with Active hydrogen compounds:

Chlorosulphonyl isocyanate undergoes the expected nucleophilic additions with alcohols, thiols, phenols and amines[8-10].

The resulting N-chlorosulphonyl derivative can be easily functionalized by reacting with water/alcohol/amine (Scheme I.1). Thus, the use of CSI enables the formal insertion of $-CONHSO_2-$ linkage between alcohol, and/or amine functional groups.

Scheme I.1

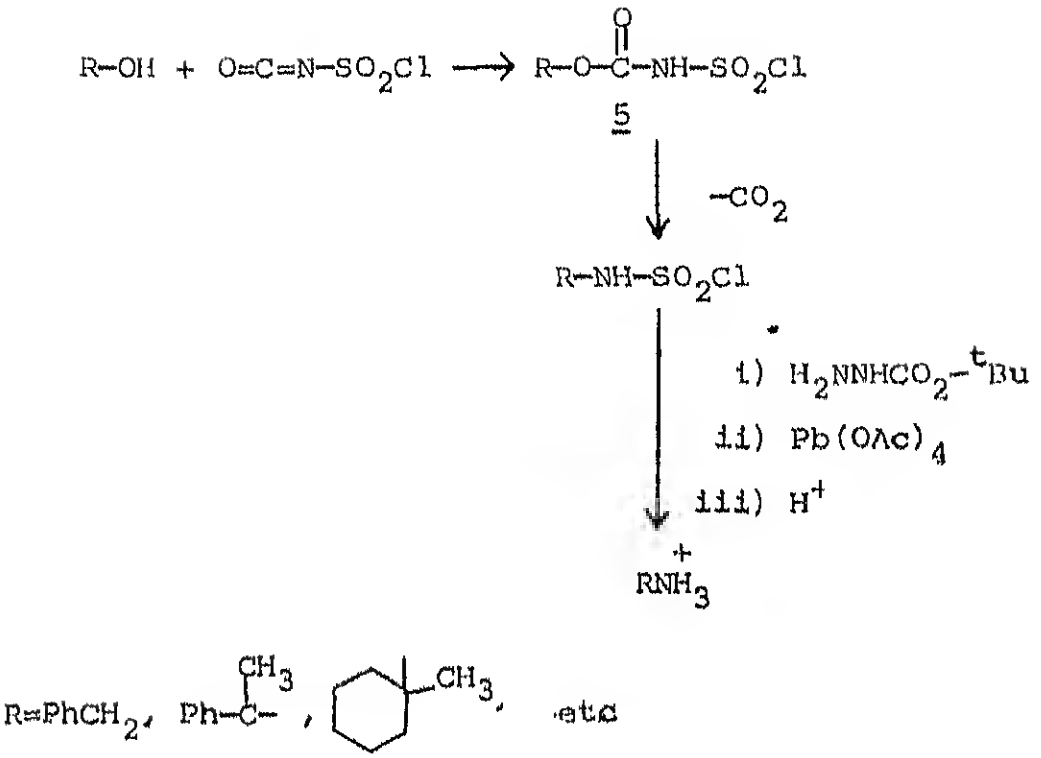


R=H, alkyl, aryl etc.

X=O, NH, NR^1, S.

The facile reactions of CSI with alcohols have been exploited in their conversion to the corresponding amines.[11] This mainly applies to tertiary and benzylic alcohols, ROH, in which the alkyl portion R is able to support a positive charge (Scheme I.2). A simple synthesis of oxazolidones[12] is possible by the reaction of CSI with α-ketoalcohols (Scheme I.3).

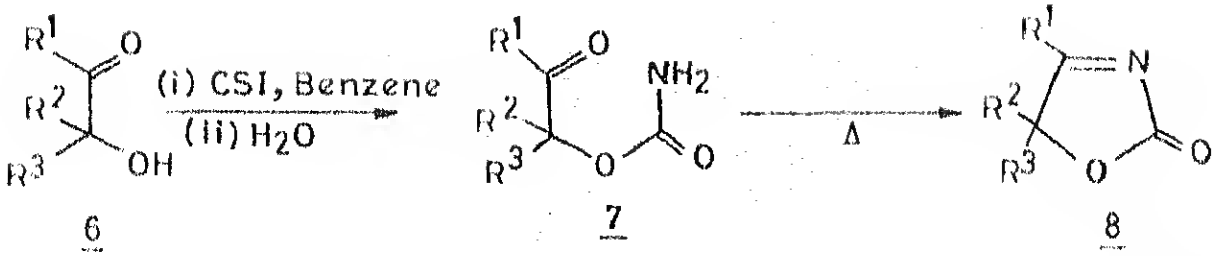
Scheme I.2



The exceptional reactivity of CSI with alcohols makes it possible to derivatize primary alcohols in the presence of other functionalities. This has been utilized in the synthesis of (±)-1-carba analogues of cefoxitin (10)[13,14] (Scheme I.4).

The reaction of phenols with CSI, at ordinary temperatures, is quite analogous to that of alcohols. But at elevated temperature the reaction affords a new class of reactive isocyanates, viz., aryloxysulphonyl isocyanate 13 which on hydrolysis yield aryl esters of sulphamic acid (14)[15] (Scheme I.5).

SCHEME I.3

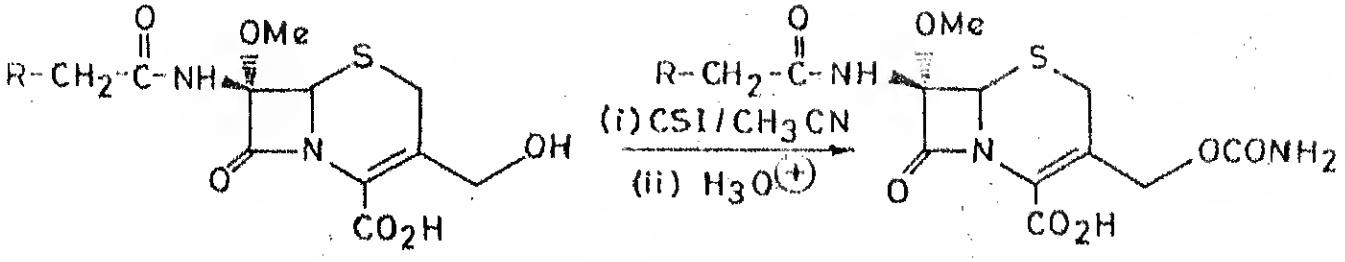


6 7 8

R^1 = ph , t - Bu

R^2, R^3 Me, ph

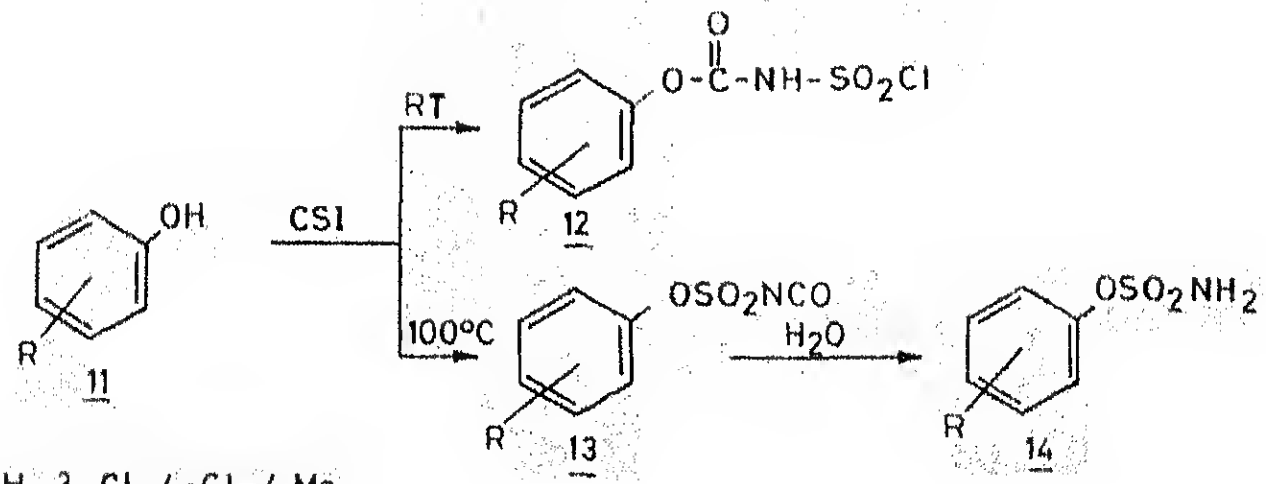
SCHEME I.4



9 10

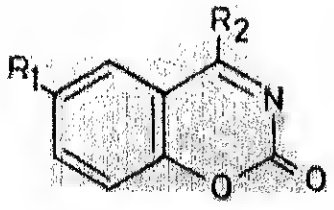
R = 2 - thienyl

SCHEME I.5



11 12 13 14

R = H , 3 - Cl , 4 - Cl , 4 - Me , 4 - OMe , 4 - CN



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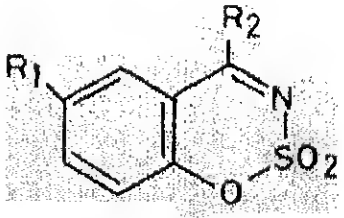

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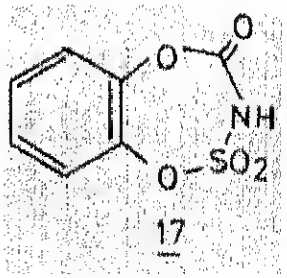

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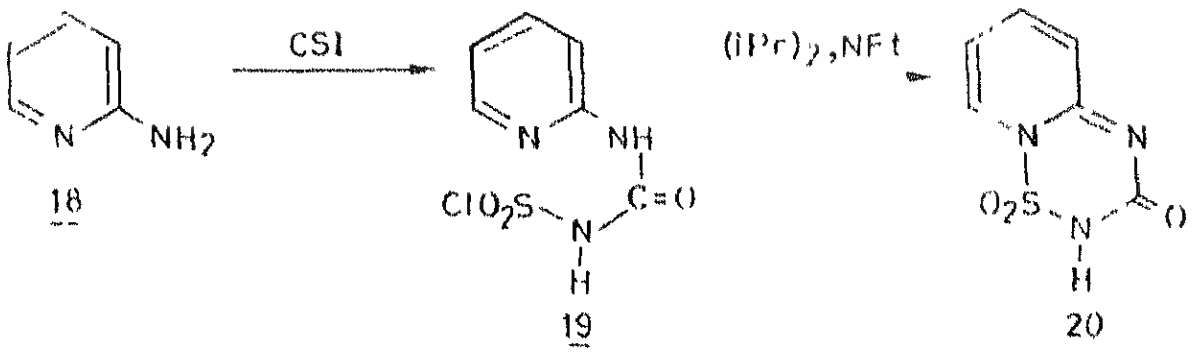
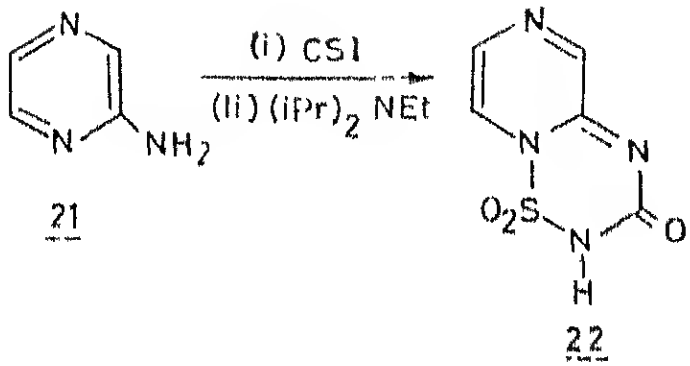
Salicylaldehydes and o-hydroxyacetophenones react with CSI, at room temperature, to give benzoxazinones (15).[16] The same reaction, in refluxing toluene, affords 1,2,3-benzoxathiazine-2,2-dioxides (16)[17] in good yields. Similarly, CSI reacts with catechols to give a new series of seven-membered heterocycles viz., the benzo-(f)-2,2,4-trioxo-1,5,2,3-dioxathiazepins (17).[18]

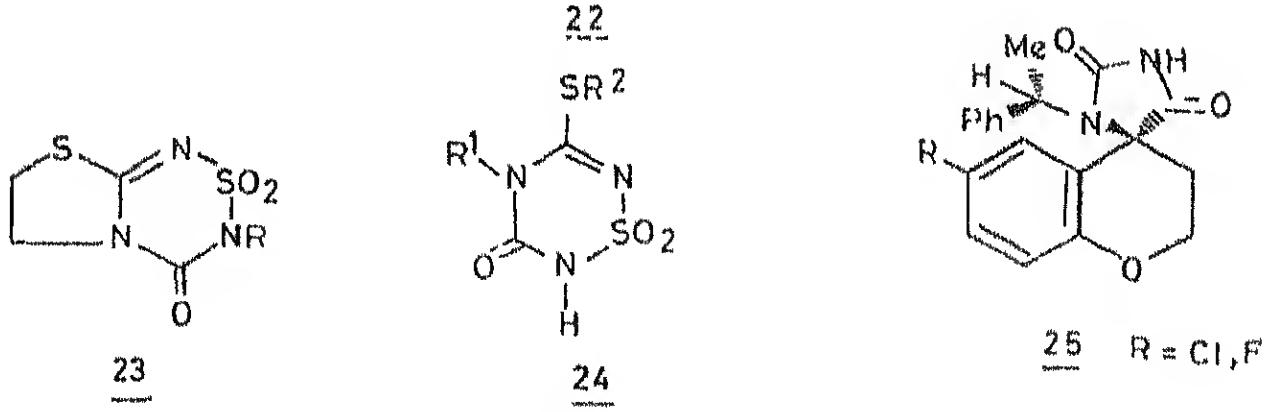
The facile reaction of CSI with amines has been exploited in the syntheses of some heterocyclic compounds. For example, Karady et al.[19] have reported the reaction of CSI with 2-aminopyridine (18) and 2-aminopyrazine (21). The intermediate 19 formed in this reaction, undergoes smooth cyclization in the presence of ethyldiisopropylamine to give the triazine 20 (Scheme I.6). Likewise, thiatriazine derivatives 23 and 24 can be prepared by the reaction of isothioureas with CSI.[20] Sterically hindered α-amino nitriles react with chlorosulphonyl isocyanate to give, after hydrolysis, the corresponding hydantoins. This has been utilized in the synthesis of optically active spiro-hydantoins (25).[21]

A new synthesis of 1,2,4-benzothiadiazines (28) has been achieved by the reaction of aniline and substituted anilines with CSI, followed by a Friedel-Crafts Cyclization[22] (Scheme I.7).

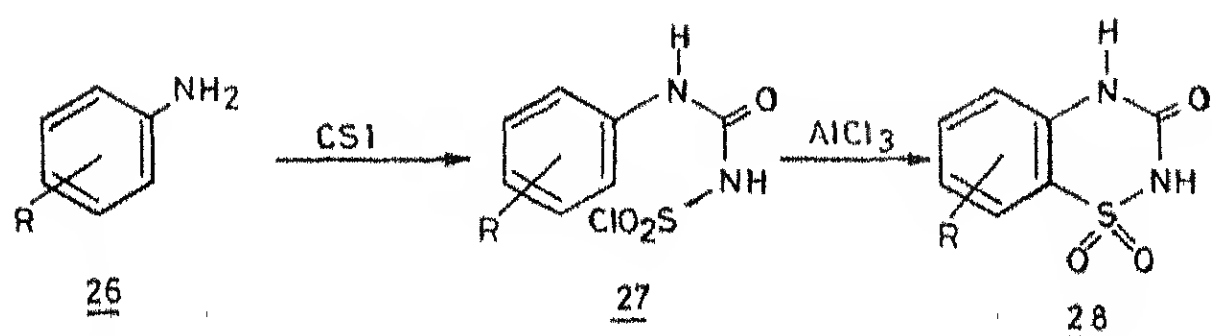
SCHEME 1.6







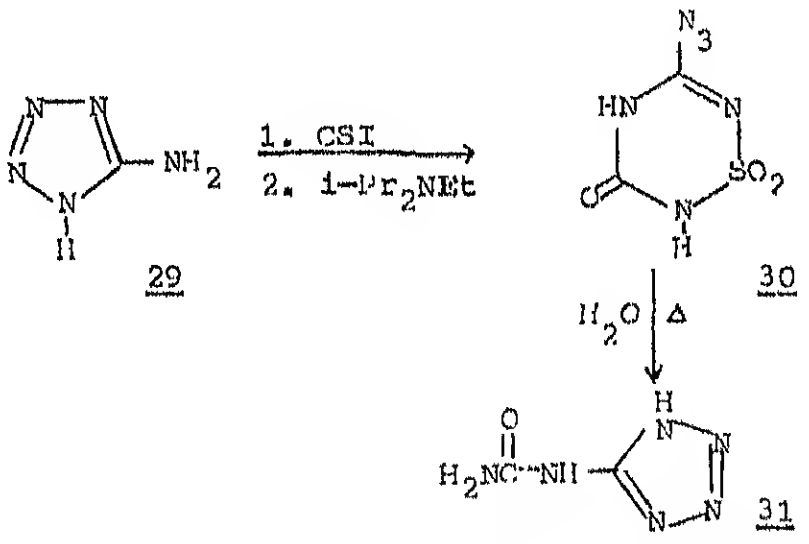
SCHEME 1.7



R = H, 4-Me, 2-Me, 4-Cl, 3-Br, 4-OMe.

The reaction of CSI with 1H-tetrazol-5-amine (29)[23] and subsequent treatment with a hindered base, ethyldiisopropylamine, affords an interesting thiatriazine derivative 30. Brief treatment of 30 with boiling water converted it in to the urea 31 in which the tetrazol system was reconstituted (Scheme I.8).

Scheme I.8



Recently, Olah et al.[24] have used CSI in converting aldoximes and amides into nitriles, thus employing it as a dehydrating agent.

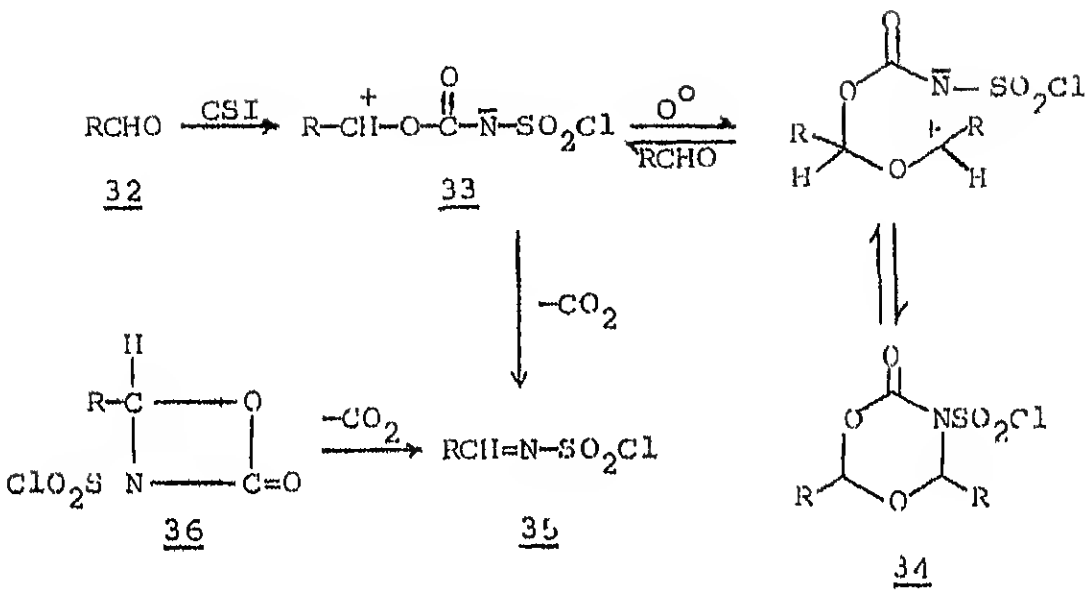
Carboxylic acids react readily with CSI to form a relatively unstable intermediate, which then loses carbon dioxide to give the corresponding N-chlorosulphonyl carboxamides[25]. These carboxamides can in turn be converted, *in situ* to nitriles in good overall yields, by treatment with dimethylformamide. Chlorosulphonyl isocyanate has been found to be

good reagent for the conversion of carboxylic acids to the corresponding anhydrides, amides and esters.[26] Both aliphatic and aromatic carboxylic acids have been found to undergo smooth transformation in the presence of carboxylic acids, aliphatic and aromatic amines, alcohols and phenols to give the corresponding anhydrides, amides and esters in good yield.

Reactions with Carbonyl Compounds:

The cycloaddition to sulphonyl isocyanates across carbon oxygen double bond in aldehydes and ketones is a useful method for the synthesis of sulphonylimines. Graf has reported[27] the formation of N-chlorosulphonyl azomethine, when CSI reacts with aldehydes, at room temperature. The azomethine derivative may be considered to be formed from (2+2) cycloaddition product followed by loss of carbon dioxide. On the basis of spectroscopic methods it has been shown that, at low temperature, CSI reacts with benzaldehyde and acetaldehyde (molar ratio, 1:2) to give the corresponding derivatives of dioxazine (34).[28]

Scheme I.9



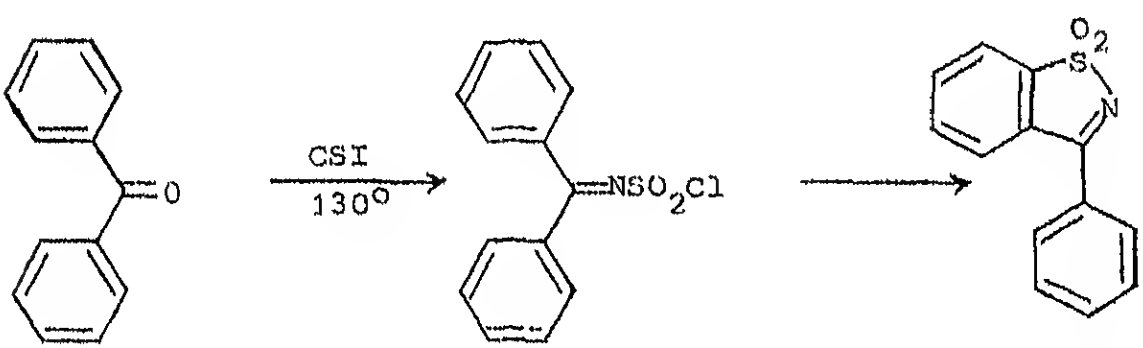
The formation of 34 favours the intermediacy of the 1,4-dipolar species 33. However, the exact rate of carbon-nitrogen bond formation in relation to carbon dioxide elimination is difficult to determine and therefore, the transient formation of the oxazetidinone 36 cannot be ruled out (Scheme I.9).

The reaction of CSI with ketones is, however, more complicated. The reaction products with different structural features have been isolated, depending upon the structures of ketones, concentration of the reactants and the experimental conditions employed.

Equimolar reaction of CSI with 1,2-diphenylcyclopropane,[29] tropone,[30] 2,6-diphenyl-4(H)-pyran-4-one[31] and flavone[31] led to

the formation of the corresponding indinesulphonyl chlorides. Benzophenone reacts with CSI, at elevated temperature, to form benzothiazole-1,1-dioxide, via the intermediate azomethine[28] (Scheme I.10).

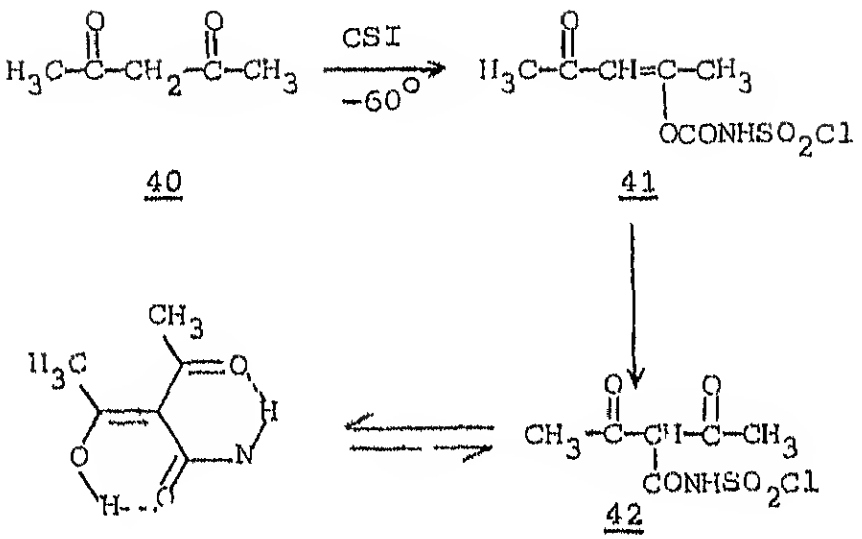
Scheme I.10



37 38 39

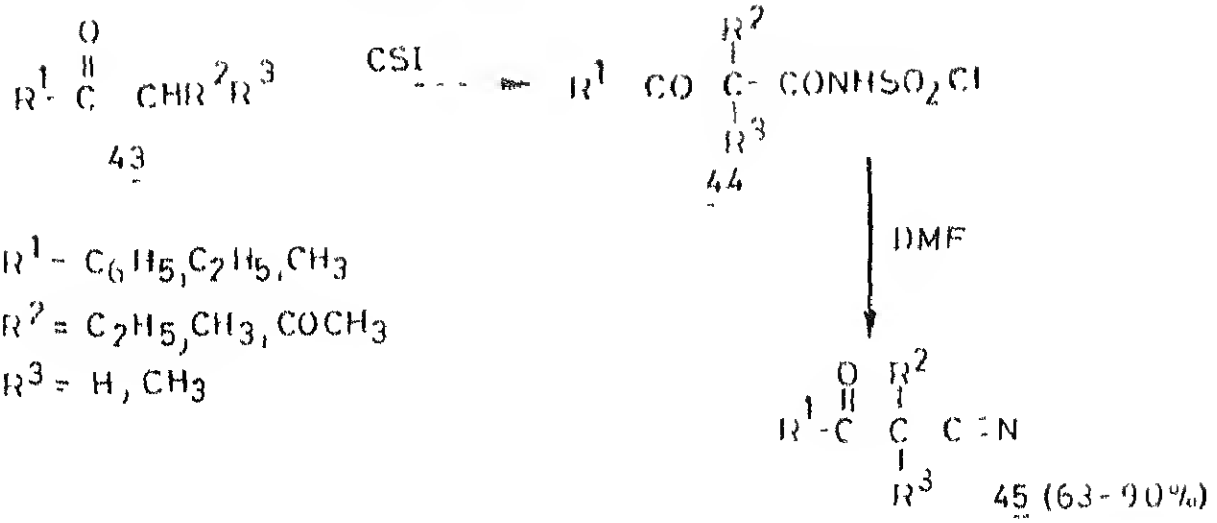
Acetylacetone, reacts with CSI to produce the enol carbamate 41 in 87% yield, at low temperature. The compound 41 rearranges, on warming in solution to 42, via an elimination reaction and readdition of CSI (Scheme I.11).[28] β-Ketocarboxamide 42 is, however, formed when the above reaction is carried out at room temperature.

Scheme 1.11

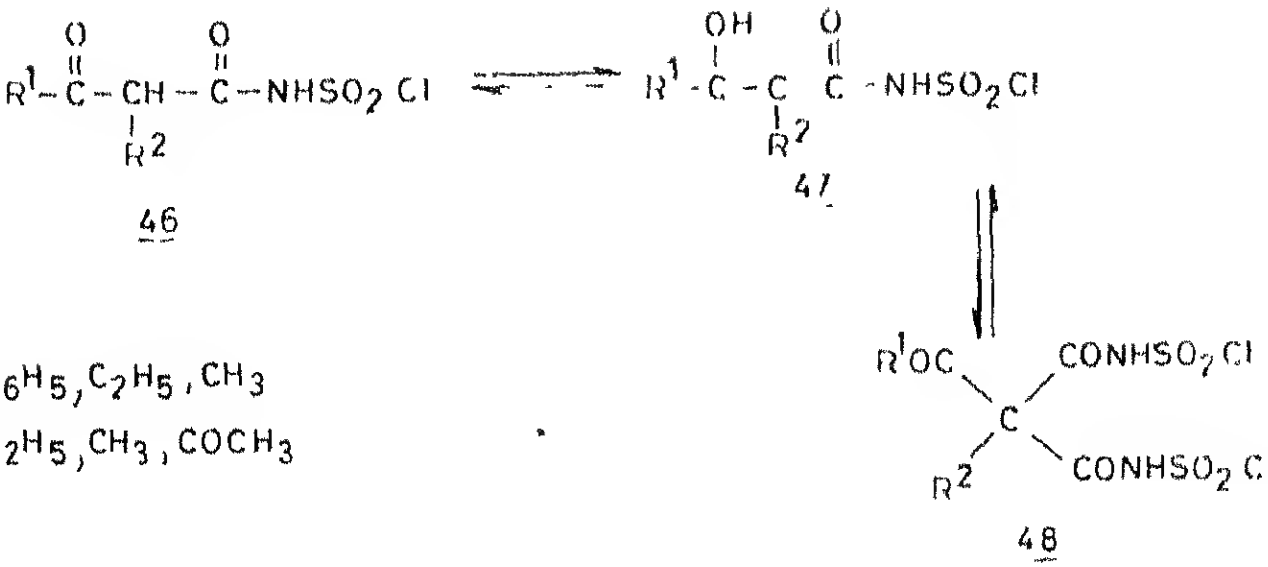


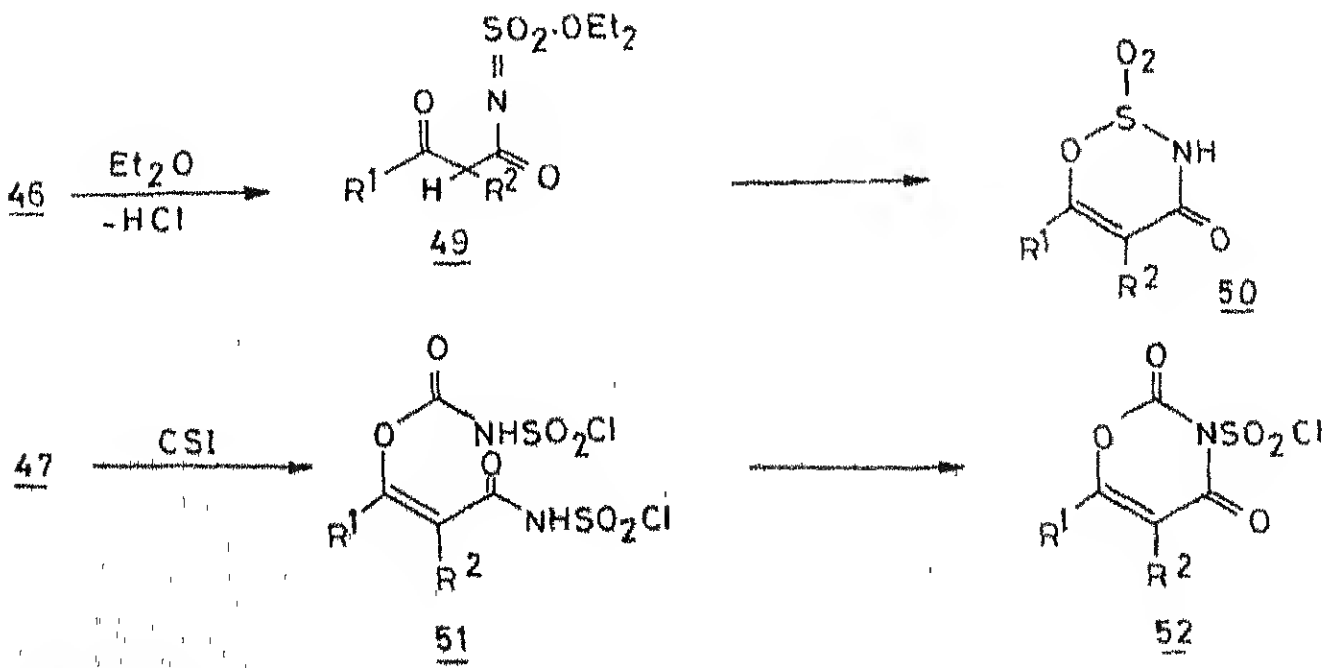
Enolizable ketones undergo electrophilic reaction with CSI to produce N-chlorosulphonyl-β-ketocarboxamides, 44.[28,32] These compounds can be converted, by treatment with DMF, into the corresponding β-ketonitriles 45 in high yields (Scheme I.12).[33] Under appropriate conditions, β-ketoamides (46) obtained from aliphatic and aromatic ketones, can undergo further transformation, which involves a second electrophilic addition of CSI to the enol tautomer, to produce malonamide derivative 48. Hassner and Rasmussen reported,[34] for the first time, the electrophilic addition of CSI to simple ketones, which provides a facile entry into the 3,4-dihydro-4-oxo-1,2,3-oxathiazine-2,2-dioxide (50) and 3,4-dihydro-2H-2,4-dioxo-1,3-oxazine (52). When ether is used as a solvent, CSI acting as a Lewis acid[35] can abstract a chloride from 46, thus producing 49 which in turn gives 50 by a proton transfer and ring closure.

SCHEME 12



SCHEME 13



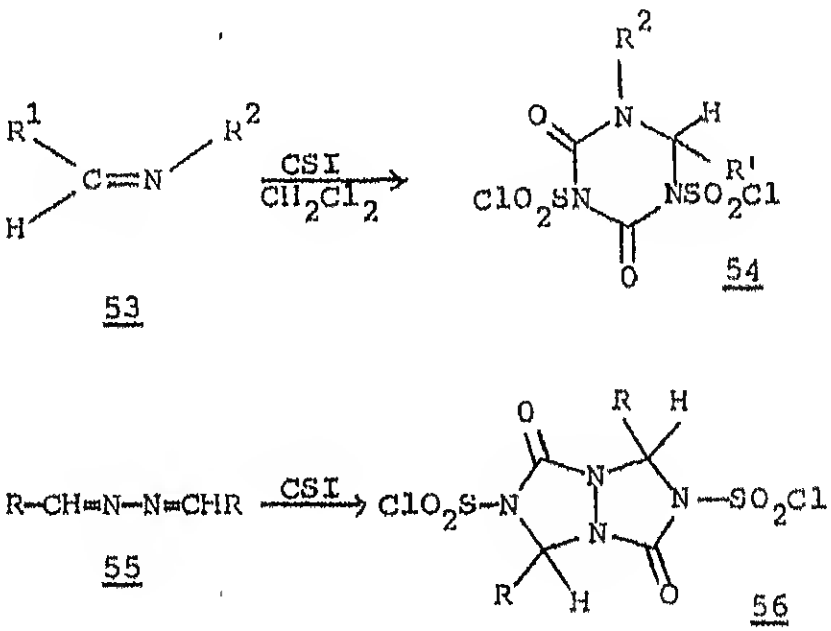


CSI reacts with 47 to produce enolcarbamate (51) and this cyclizes with loss of sulphamoyl chloride to furnish 52, in fairly good yield (Scheme I.13).

Reactions with Carbon Nitrogen double bonds:

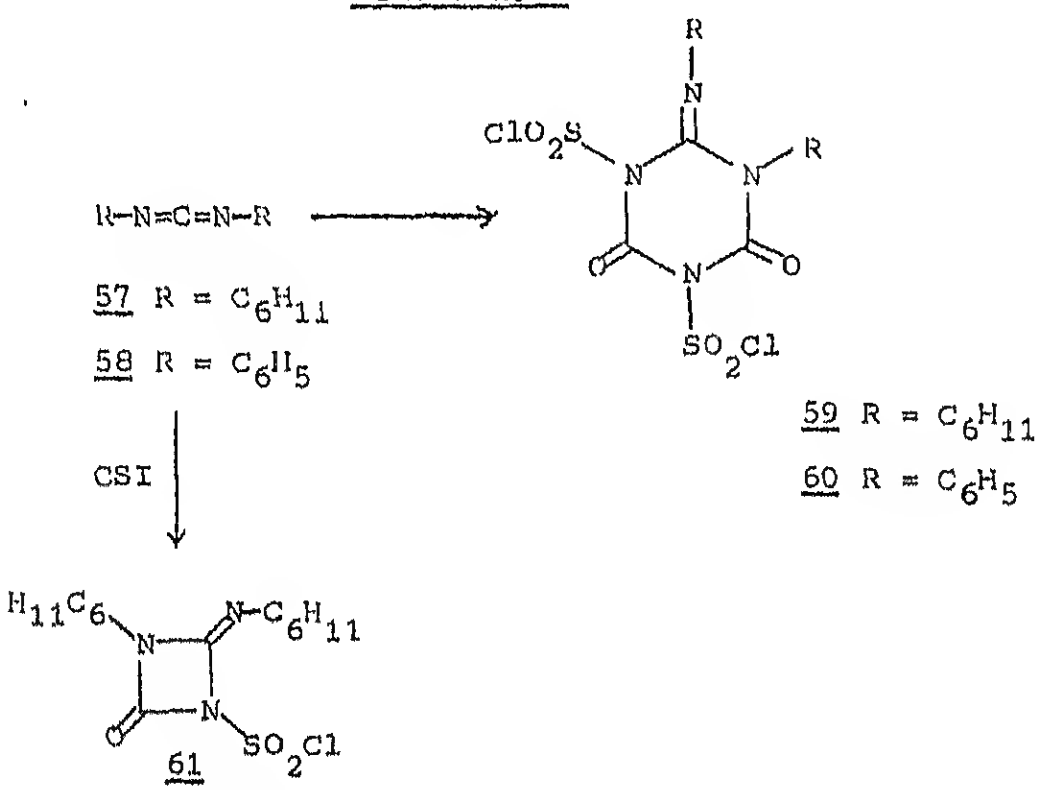
Suschitzky et al.[36] have made a detailed investigation on the reaction of CSI with carbon nitrogen double bonds. Schiff bases react with CSI in a 1:2 molar ratio to produce triazindiones, whereas azines (which can be regarded as bis-anils) react with CSI to give bicyclic tetraza-compounds 56 (Scheme I.14).

Scheme I.14



The dropwise addition of CSI to the diimide 57 is reported[36] to yield the diazetidinone 61, while with inverse addition a 2:1 CSI-diimide adduct triazinedione 59 was obtained. However, it is interesting to note that diphenylcarbodiimide 58 gave triazinedione, 60, regardless of the mode of addition[36] (Scheme I.15).

Scheme I.15

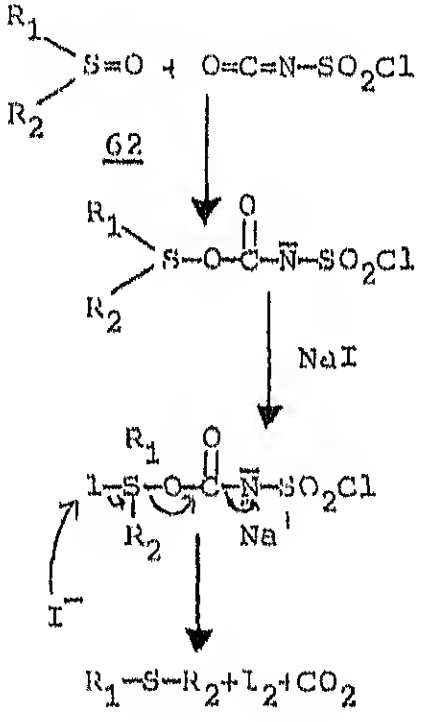


Reaction with sulphur oxygen double bonds:

Dimethyl sulphoxide reacts with CSI at low temperature, to form N-chlorosulphonyldimethyl sulphimide[5], by the elimination of carbon dioxide from the initially formed CSI-DMSO adduct.

Koshavamurty et al.[37] have found that CSI/NaI reagent system to be very efficient for the reduction of sulphoxides to sulphides (Scheme I.16).

Scheme I.16

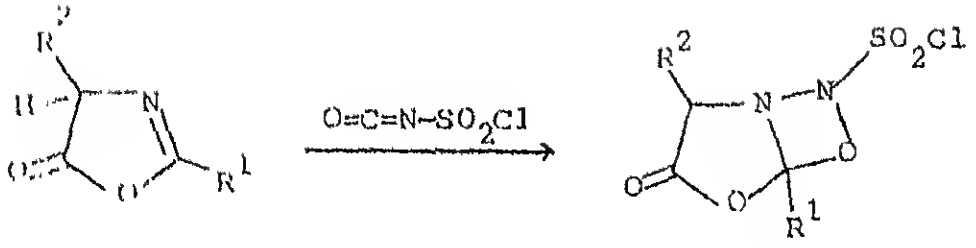


62

63

Raghunathan et al.[38] have studied the reaction of chlorosulphonyl isocyanate with 5-oxazolones. These compounds undergo a facile reaction with CSI to form a [2+2] adduct, the C=O function of CSI adding across (C=N) bond of oxazolones to form a novel bicyclic system as shown in Scheme I.17.

Scheme I.17



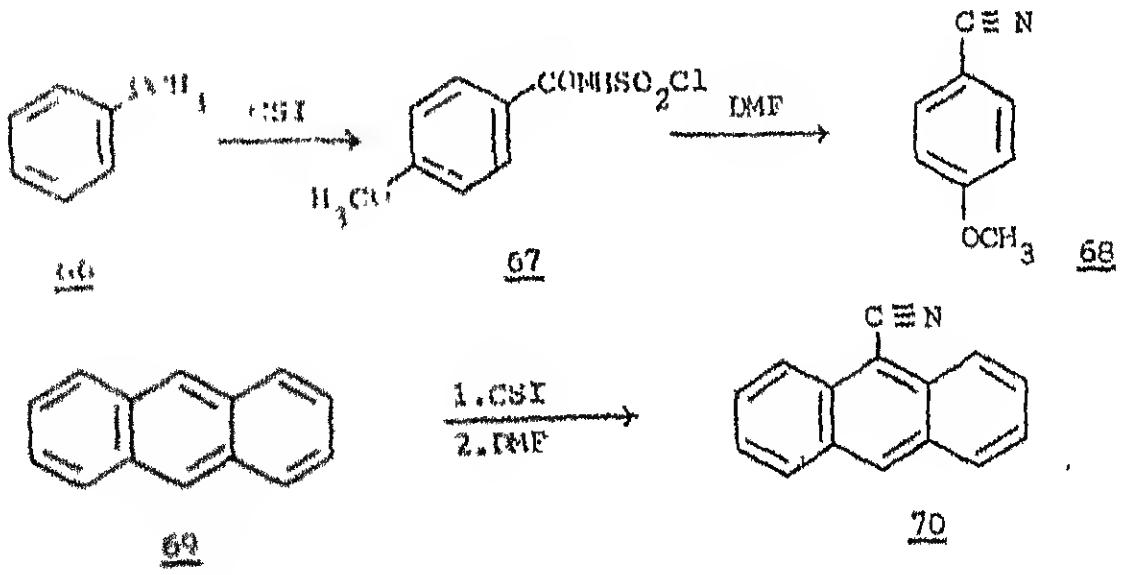
64 65

$R^1 = C_6H_5$, $R^2 = CH_3$

I.2 Reactions with Aromatic Compounds

Aromatic compounds which readily undergo electrophilic substitution, react with CSI to produce the corresponding N-chlorosulphonyl carboxamides. These can in turn, be converted to the corresponding nitriles by reacting with DMF[39] (Scheme I.18).

Scheme I.18



66 67 68

69 70

This reaction is of synthetic importance, as it provides a simple one-pot-method for the preparation of aromatic nitriles. A 1:2.3 mole reaction of pyrrole with CSI affords 2,4-dicyano-pyrrole (71) in excellent yields, when DMF is used as a solvent.[40] On the other hand, the Vilsmeier-complex of pyrrole-2-aldehyde (72) on treatment with CSI yields an unusual product, viz., 4-chloropyrrole-2-aldehyde[41] (Scheme I.19).

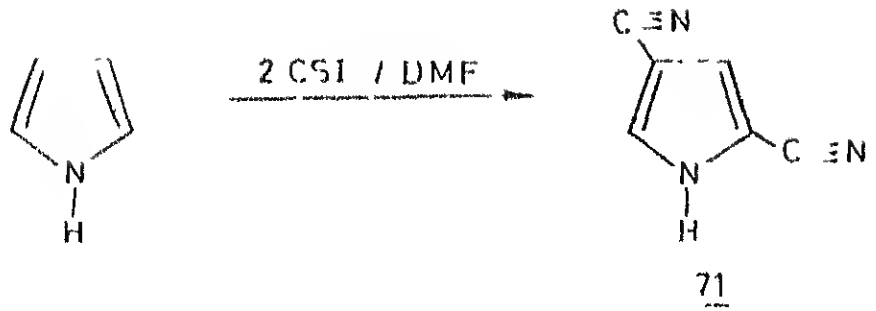
The reaction of indole with CSI affords N-chlorosulphonyl indole-3-carboxamide (75) in good yield. 75 can either be converted to the corresponding amide 76 or to the nitrile 77 in good overall yields[42] (Scheme I.19). Similarly, in case of N-phenyl-2-pyrazolines, CSI undergoes electrophilic substitution at the p-position of the N-phenyl group[43] (Scheme 1.20).

I.3 Reactions with Multiple Bonds

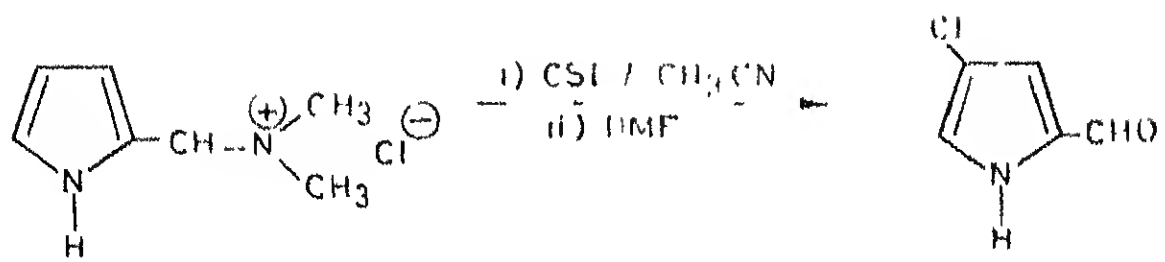
I.3.1 Reactions with carbon-carbon multiple bonds

From the synthetic point of view, the cycloaddition reactions of CSI with carbon-carbon multiple bonds are of special interest, as they represent a novel method of preparing cyclic compounds, which are not easily accessible by other methods. A brief review of such reactions described below, will exemplify the uniqueness of CSI in forming such ring compounds.

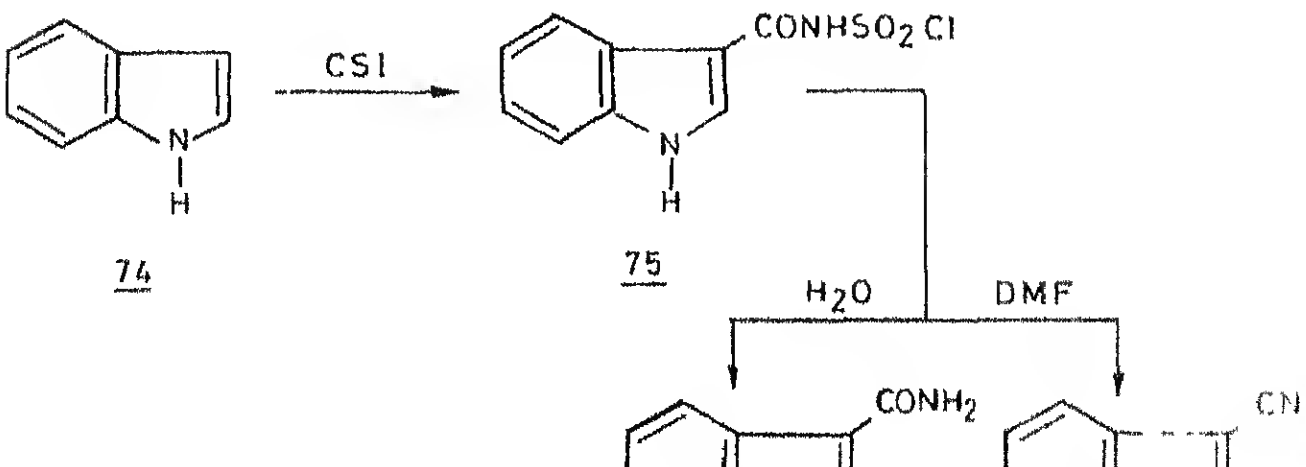
SCHEME I.19



71

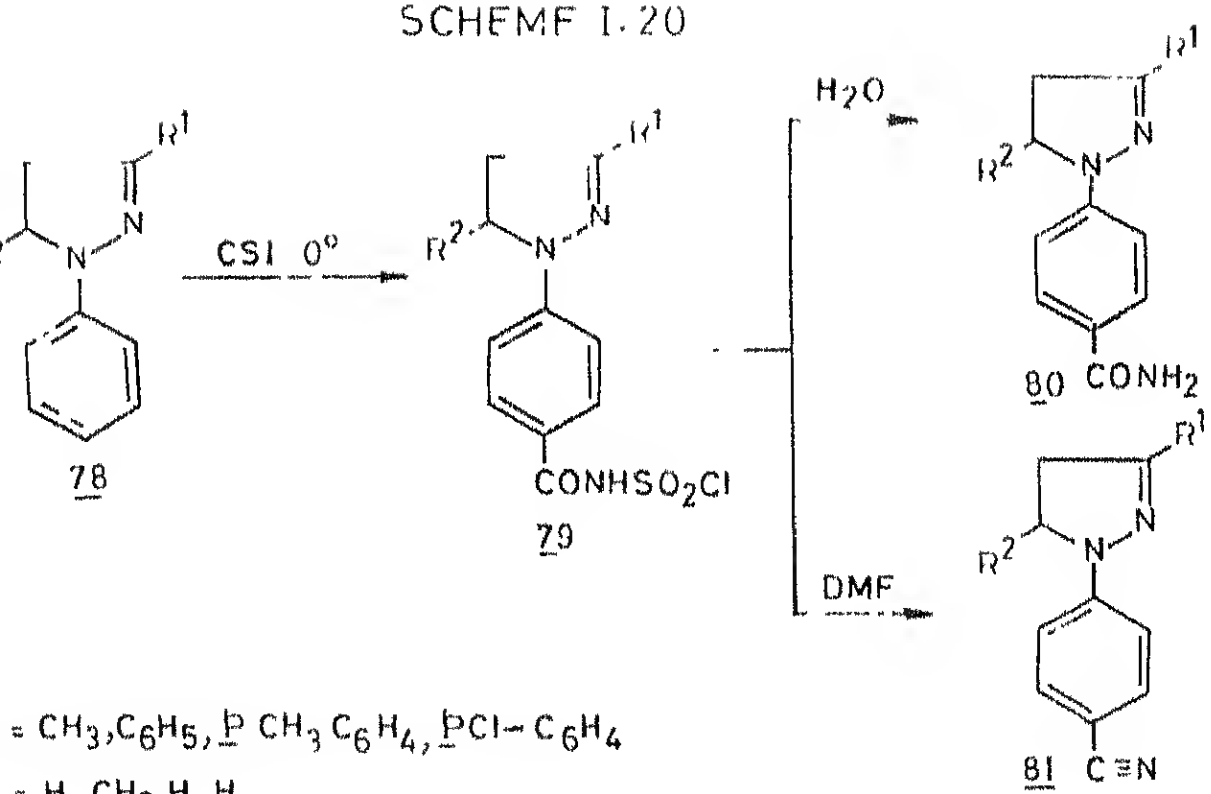


72 73



74 75 76 77

SCHEME I.20



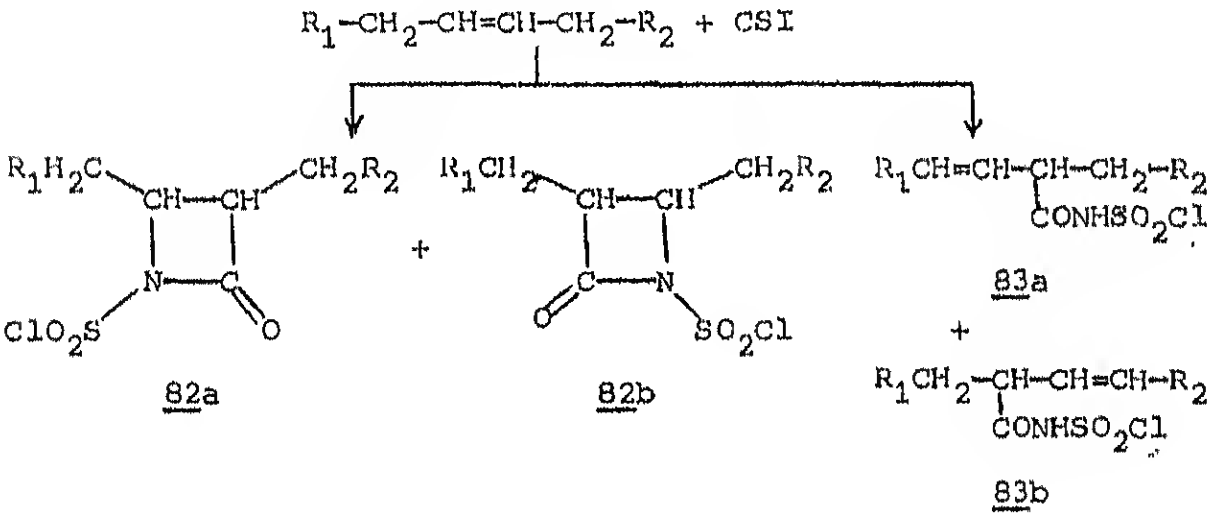
78 79 80 81

= CH_3, C_6H_5, P $CH_3C_6H_4$, P ClC_6H_4

= H, CH_3, H, H

The extraordinary propensity of CSI to add to carbon-carbon multiple bonds are well decumented.[4-8] CSI reacts with olefins forming 1:1 cyclic and linear adducts,[39] viz., N-chlorosulphonyl-β-lactam(82a and 82b) and N-chlorosulphonyl carboxamide (83a and 83b) as illustrated in Scheme I.21. The ratio of products (cyclic to linear adducts) depends upon the constitution of the olefin. On the basis of infrared spectral studies[7] it has been concluded that the N-chlorosulphonyl-β-lactam (82a and 82b) and the open chain N-chlorosulfonyl carboxamide (83a and 83b) are formed independently. The ratio in which the products are formed remain constant from the beginning to the end of the reaction.

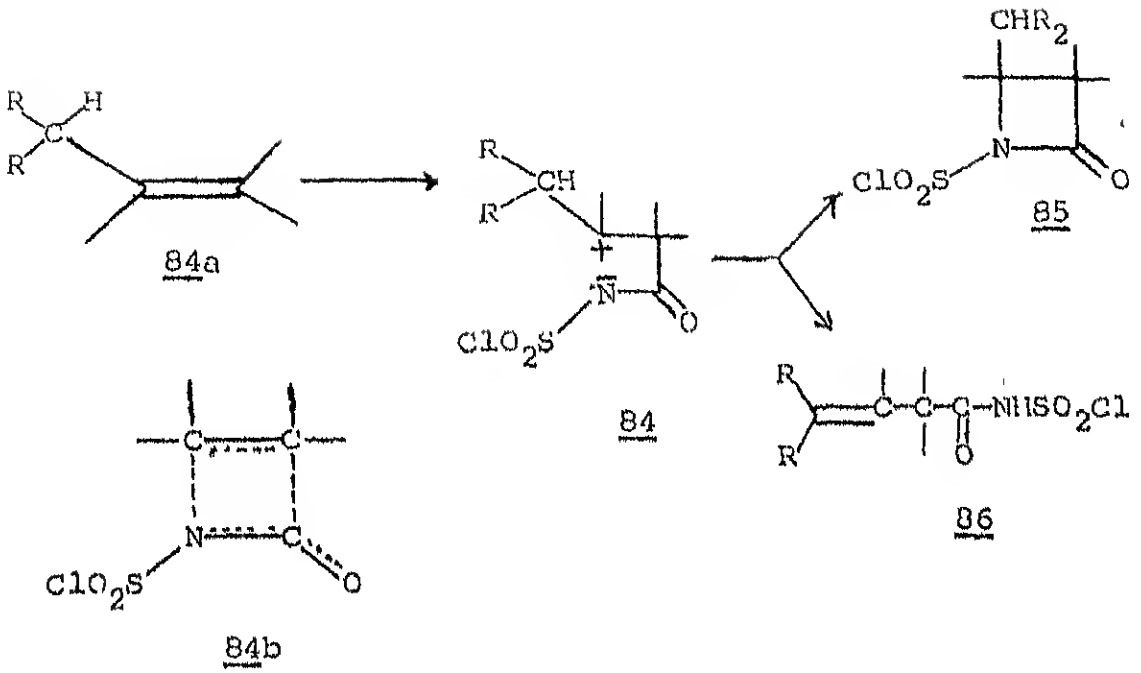
Scheme I.21



Both concerted and non-concerted mechanisms have been postulated for these reactions. Graf[6] envisaged a two step

mechanism for CSI-olefin reactions, involving the initial formation of 1,4-dipolar adduct 84, which could stabilize itself through cyclization to the four membered 85 and/or via a proton shift to 86. This proposal finds support from the following observations. i) The influence exerted by the nature of the olefin and the polarity of the solvent on the rate of the reaction,[44] ii) independent formation of 85 and 86, and their relative proportions being independent of the change in the reaction conditions. Moriconi,[45] on the other hand, has proposed a near concerted, thermally allowed $\pi^2s + \pi^2a$ cycloaddition, probably initiated by π-complex formation and proceeding through the polar transition state 84a. Among the evidences cited in favour of this rationale are; i) the lack of rearrangement in the reaction of CSI with rearrangement-prone bridged bi- and tri- cyclic olefins, ii) the stereospecific addition of CSI to cis- and trans-olefins, and iii) the initial formation of (2+2) cycloadduct with conjugated dienes, which readily rearrange to more stable (4+2) adducts (Scheme I.22).

Scheme I.22

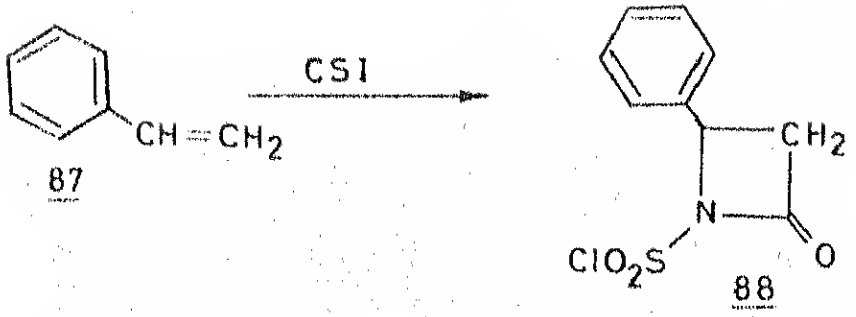


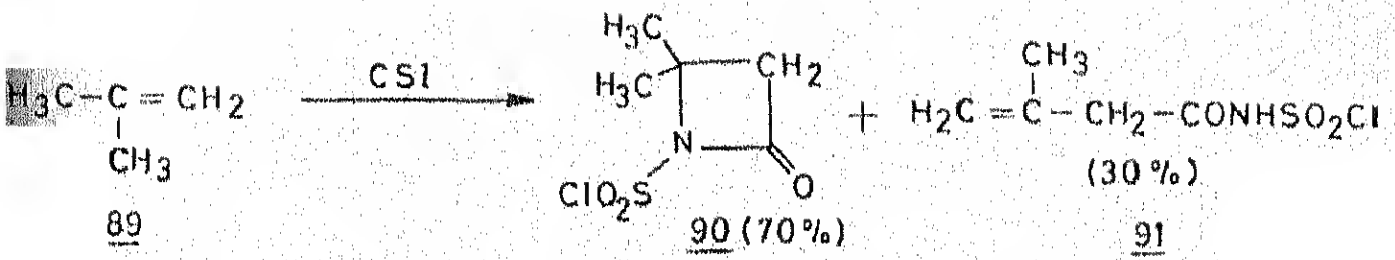
Thus, the cycloaddition[15-50] is found to be highly stereo- and regiospecific. In other words, the cis-adduct is always formed and the addition takes place in such a way that the most stable carbonium ion would be generated. The examples quoted in Scheme I.23 highlight the reaction of CSI with mono-olefins.

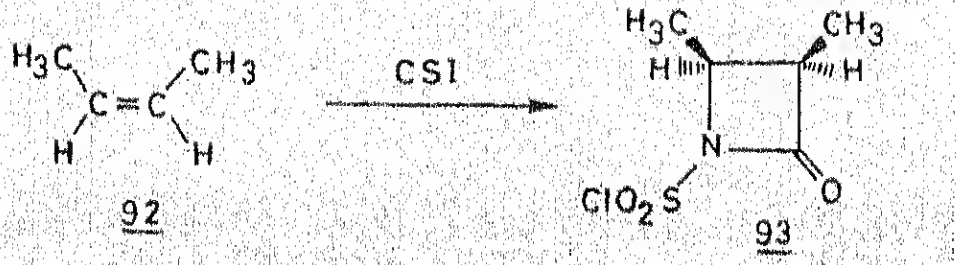
Recently, Suschitzky et al.[51] have reported that o-dialkylaminostyrenes react with CSI in 1:2 mole ratio to yield 6-(o-dialkylaminophenyl)uracils (112), after hydrolysis.

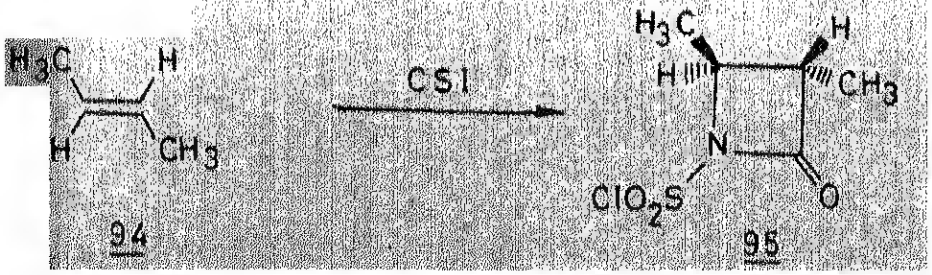
There are several reports in recent years about the remarkable utility of chlorosulphonylisocyanate in the total

SCHEME I.23

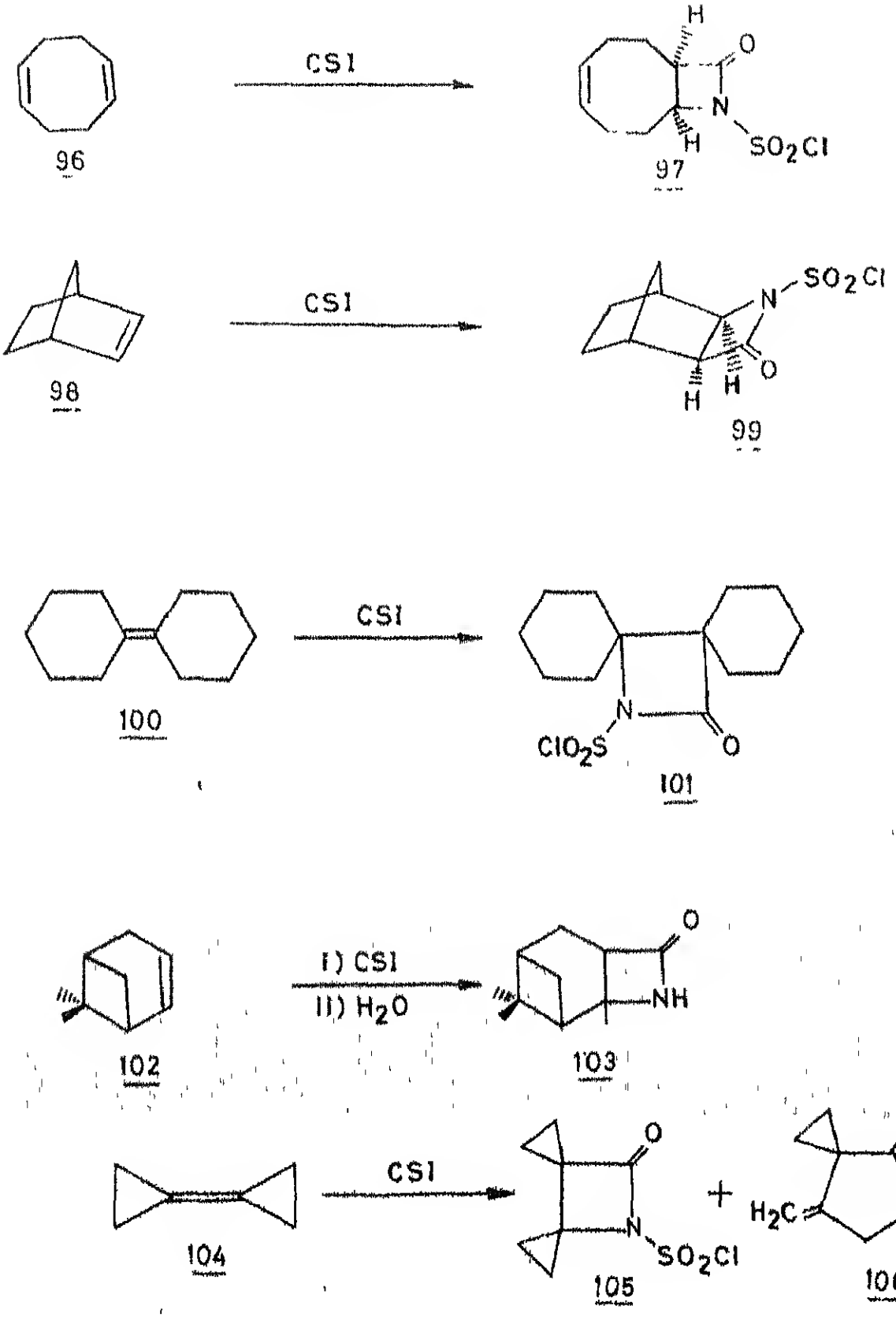

CSI
CH=CH2
87
CH2
N
ClO2S
O
88


H3C-C=CH2
CH3
89
CSI
H3C
H3C
CH2
N
ClO2S
O
90 (70%)
+
CH3
H2C=C-CH2-CONHSO2Cl
(30%)
91


H3C
CH3
C=C
H
H
92
CSI
H3C
CH3
H
H
N
ClO2S
O
93

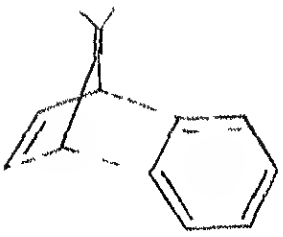

H3C
H
H
CH3
94
CSI
H3C
H
H
CH3
N
ClO2S
O
95

SCHEME I.23



contd.

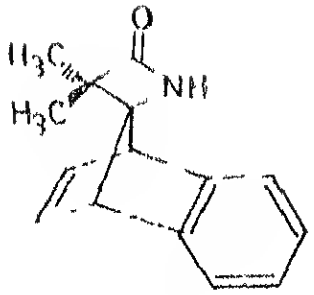
SCHEME I.23



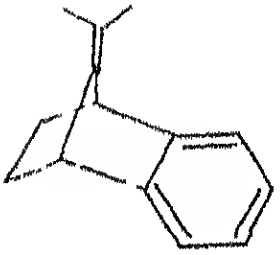
107

i) CSI

ii) Na_2SO_3 / $OH^{(-)}$



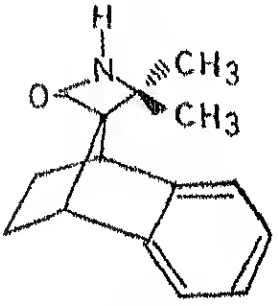
108



109

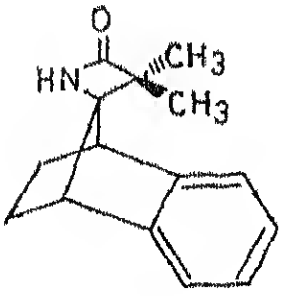
i) CSI

ii) Na_2SO_3/ $OH^{\ominus}$

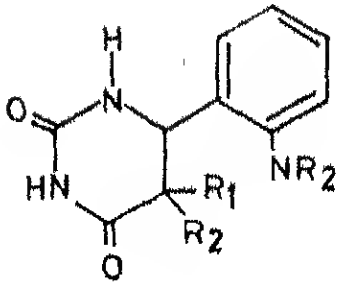


110

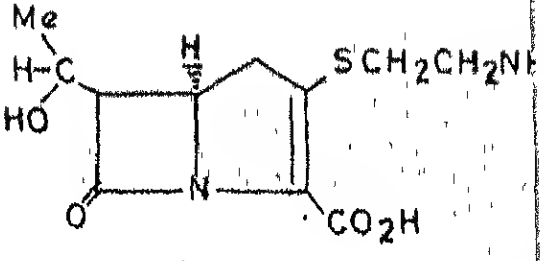
+



111



112



113

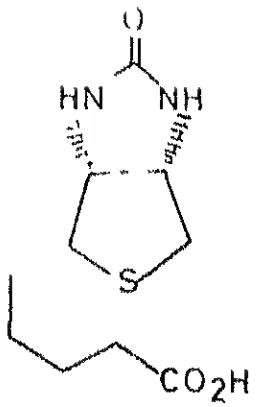
cont

Synthesis of many natural products and their derivatives. These include antibiotics such as penicillin[52-55] and cephalosporin analogues,[56-58] thienamycin[59,60] (113), β-lactam prostoglandins,[61] (±)-biotin[62] (114), dethiobiotin[63] (115), and dl-daunosamine[64] (116). In all these syntheses, a crucial step involves the β-lactam formation using CSI.

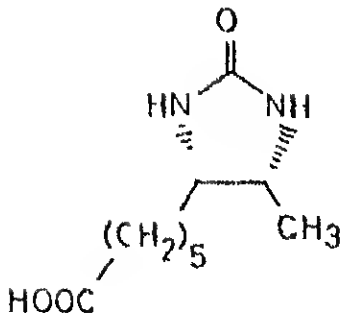
The reaction of CSI with 1,3-dienes and trienes are well documented in literature.[65-70] These undergo 1,2- as well as 1,4-additions with CSI. A series of unique 1,2- to 1,4-rearrangements of the initially formed N-chlorosulphonyl-β-lactam have been observed in many cases. An illustrative example is depicted in Scheme I.24.

The reaction of chlorosulphonyl isocyanate with cyclic trienes, however, gave only 1,6-cycloaddition products. The 7-substituted cycloheptatrienes gave N-chlorosulphonylimino ethers.[71-72]

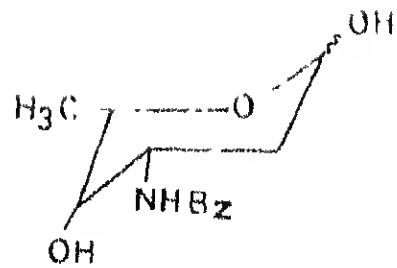
The reaction of cyclooctatetraene with CSI yielded 1,4- and 1,6-cycloadducts, which were characterized as their lactams after hydrolysis. The formation of a (2+2) cycloaddition product was also observed at low temperatures.[73] In case of polyenes, the uniparticulate electrophile, CSI, can act as an extremely useful reagent for the generation and intramolecular trapping of carbonium ions. Paquette and his coworkers[74-76] have demonstrated this use of CSI as a mechanistic probe in



114

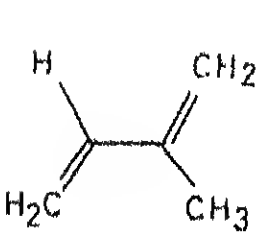


115

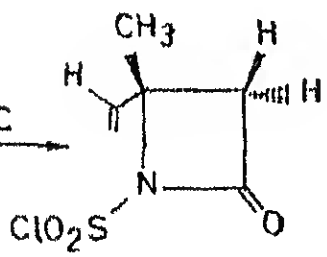


116

SCHEME 1.24



117



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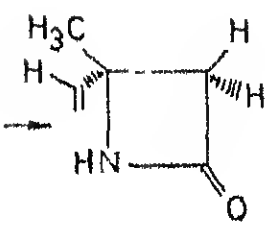

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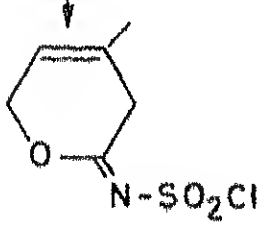

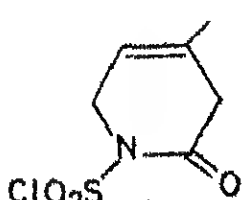

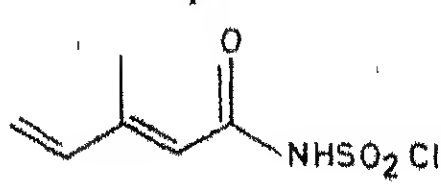

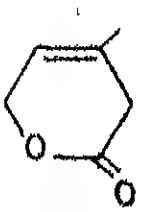

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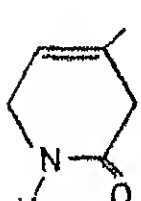

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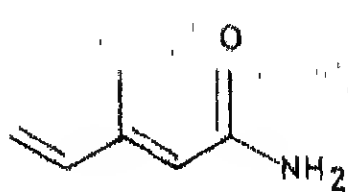


122

their studies of molecules such as bullvalene,[74] barrelene[75] and homo-barrelene.[76] A novel synthesis of methoxyazabullvalene has emerged from this research of fluxional systems[77] (Scheme I.25).

Reactions with Nitrogen-Oxygen Double bonds

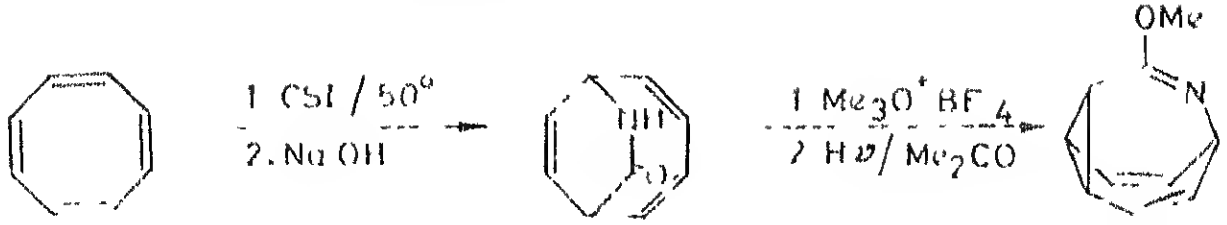
Chlorosulphonyl isocyanate has been employed by Dhar and Bag for effecting the denitrosation of N-nitroso compounds.[78] This involves the initial addition of CSI to nitroso group (Scheme I.26).

Kumar & Thamaraiselvi[79] have studied the reaction of CSI with tetracyclopentadienone, leading to the formation of stable sulphonamide. Here CSI undergoes (2+2) cycloaddition to tetracyclopentadienone.

In order to widen the knowledge of the chemistry of chloro sulphonyl isocyanate, an attempt has been made to study the reaction of this uniparticulate electrophile with various heterocycles. Investigations were carried out on the reactions of this active reagent with pyrazoles, 2-pyrazolin-5-ones, isoxazoles and 1,2,3,4-tetrahydrocarbazoles.

The pyrazoles, taken up for our present investigation for reaction with CSI include, 3,5-dimethyl-pyrazole (184a),

SCHEME 1.25



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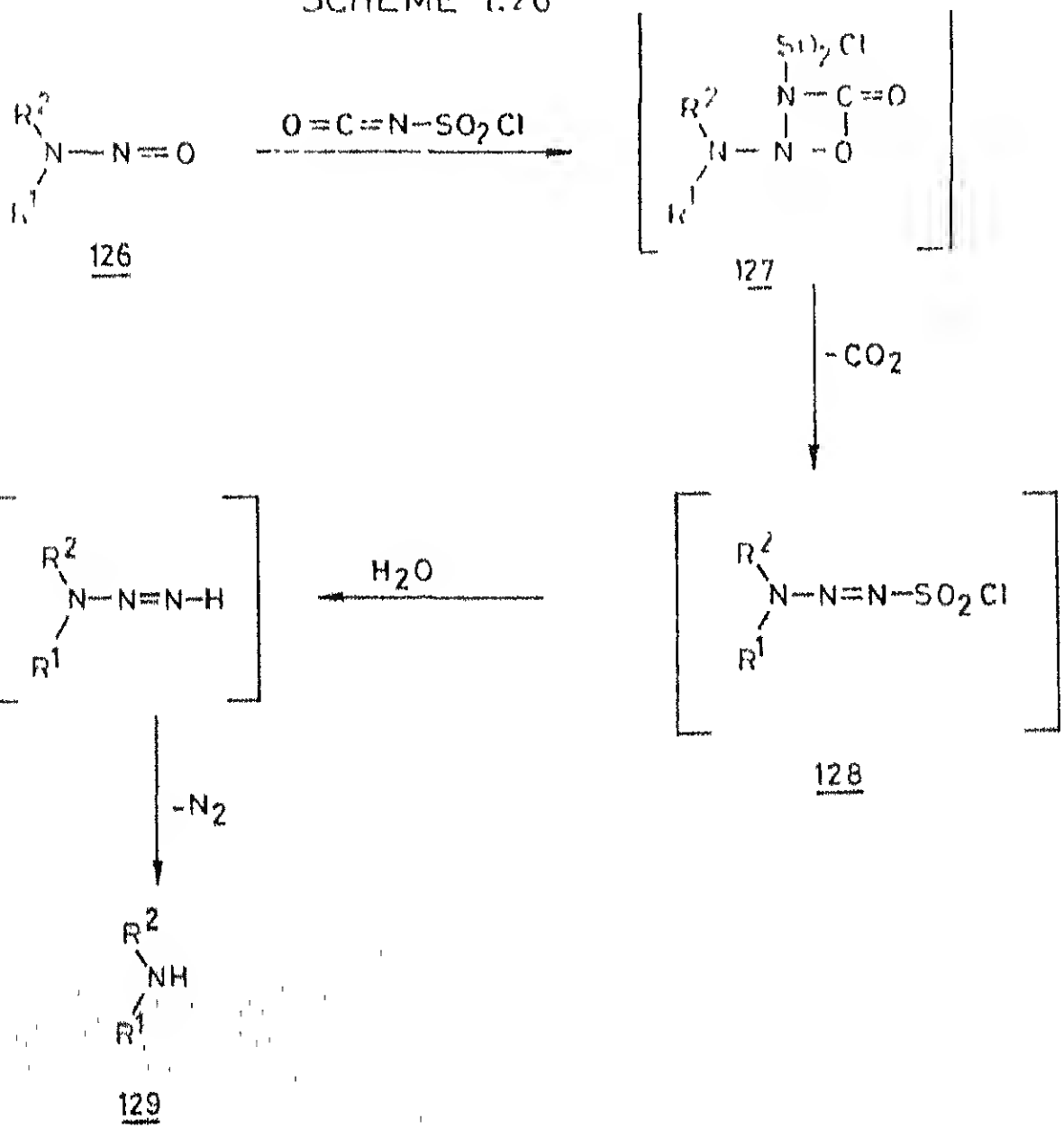
SCHEME 1.26



126 127 128 129

5-ethoxy-3-methyl-pyrazole (184b), pyrazole (184c), 1-[4-Nitro-phenyl]-3-methyl-5-ethoxy pyrazole (184d), 1-phenyl-3-methyl-5-hydroxy-pyrazole (184e), 1-[4-Nitrophenyl]-3-methyl 5-hydroxy-pyrazole (184f), 1-[2,4-dinitro phenyl]-3-methyl-5-hydroxy pyrazole (184g), 1-[4-Nitro phenyl]-3,5-dimethyl pyrazole (184h), 1-[2,4-dinitrophenyl]-3,5-dimethyl pyrazole (184i), 1-[2,4-dinitro-phenyl]-3-methyl-5-phenyl-pyrazole (184j).

2-pyrazolin-5-ones, 1,2,3,4-tetrahydrocarbazoles and isoxazoles taken for present investigation include 1-[4-Nitro-phenyl]-3-methyl-2-pyrazolin-5-one (195k), 1-[2,4-dinitro-phenyl]-3-methyl-2-pyrazolin-5-one (195l), 6,8-dinitro-1,2,3,4-tetra-hydrocarbazole (205p), 6-Nitro-1,2,3,4-tetrahydrocarbazole (205o), 3,5-dimethyl-isoxazole (199m), 4-phenyl-3-methyl-5-amino isoxazole(202n).

Reaction of 3,5-dimethyl pyrazole (184a), 3-methyl-5-ethoxy pyrazole (184b) with CSI gave rise to 3,5-dimethyl pyrazol-1-N-chlorosulphonyl-carboximide (185a), 3-methyl-5-ethoxy-pyrazol-1-N-chlorosulphonyl carboximide (185b). (185b) on alkaline hydrolysis furnished 3-methyl-5-ethoxy-pyrazol-1-N-carboximide (186b) (Scheme I.56). Pyrazole on treatment with CSI produced pyrazol-N-sulphonamide, 3,5-dimethyl-pyrazole (184a) on treatment with CSI also afforded 3,5-dimethyl-pyrazol-N-sulphonamide (188a). The reaction of 1-[4-Nitrophenyl]-3-methyl-5-ethoxy pyrazole with CSI at 0° for 0.5 hr, produced 1-[4-Nitro-phenyl]-3-methyl-5-ethoxy pyrazol-4-chlorosulphonyl carboximide.

The latter compound on alkaline hydrolysis furnished 1-[4-Nitrophenyl]-3-methyl-5-ethoxy pyrazol-4-carboximide. Treatment of 1-[4-Nitrophenyl]-3-methyl-5-ethoxy pyrazol-4-chlorosulphonyl carboximide with dimethylsulphoxide afforded the corresponding carbonitrile (Scheme I.57).

Reaction of 2-pyrazolin-5-ones (195k-l) on treatment with CSI at 0^{o}, produced corresponding 2-pyrazolin-5-imide (198k-l). Here the (2+2) cycloaddition takes place at the C=O group of the 2-pyrazolin-5-one (Scheme I.59).

Reaction of CSI with 1-phenyl-3-methyl-5-hydroxy-pyrazole (184e), 1-[4-Nitro phenyl]-3-methyl-5-hydroxy pyrazole (184f), 1-[2,4-dinitrophenyl]-3-methyl-5-hydroxy pyrazole (184g)produced the corresponding pyrazol-5-chlorosulphonyl urethane (193e-g) which on alkaline hydrolysis yielded the corresponding 5-carbamato-pyrazoles (194e-g) (Scheme I.58).

3,5-dimethyl-isoxazole, 4-phenyl-3-methyl-5-amino isoxazole on treatment with CSI gave rise to 3,5-dimethyl-isoxazol-4-sulphonamide (201m) and corresponding isoxazolyl urea respectively (204n) (Scheme I.60-61).

6,8-dinitro-1,2,3,4-tetrahydrocarbazole (205p) and 6-Nitro-1,2,3,4-tetrahydrocarbazole (205o) on treatment with CSI yielded 6,8-dinitro-1,2,3,4-tetrahydrocarbazol-N-chlorosulphonyl-carboximide and 6-Nitro-1,2,3,4-tetrahydrocarbazole-N-chlorosulphonyl-carboximide respectively. 6,8-dinitro-1,2,3,4-tetrahydro-carbazol-

N-chlorosulphonyl carboximide on hydrolysis yielded corresponding N-carboximide (207p) (Scheme I.62).

In all the above cases the 1:1 molar adduct formation has been established on the basis of mass spectroscopic data. It is interesting to note that the IR absorption band at ν 1600 cm^{-1} (>C=N) remains intact in all the adducts. This is interpreted to mean that the CST fails to react at this position of the molecule.

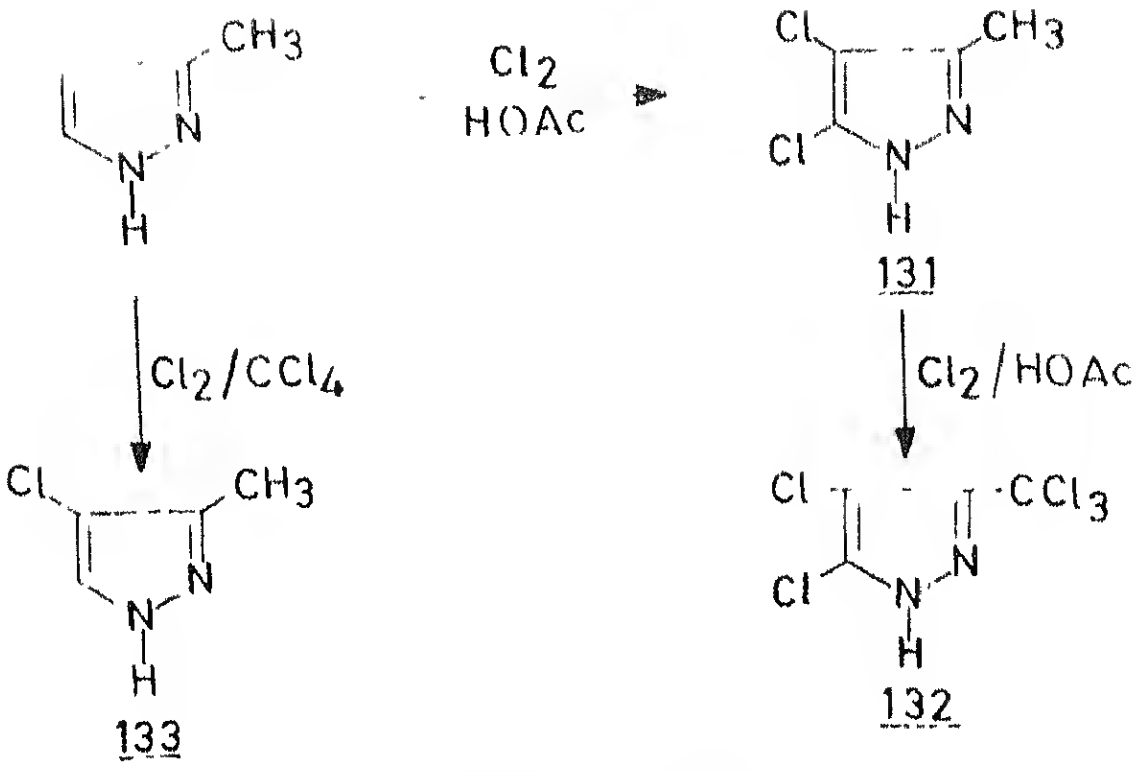
An insight into the chemical nature and reactivity of pyrazoles, 2-pyrazolin-5-ones, 1,2,3,4-tetrahydrocarbazoles, and isoxazoles will enable one to understand the chemistry of these compounds in a better way.

Knorr and Buchner, noticed that, like other aromatic compounds, pyrazole had a particularly stable nucleus and a tendency to undergo substitution[80-82]. It took place particularly in the 4th position.

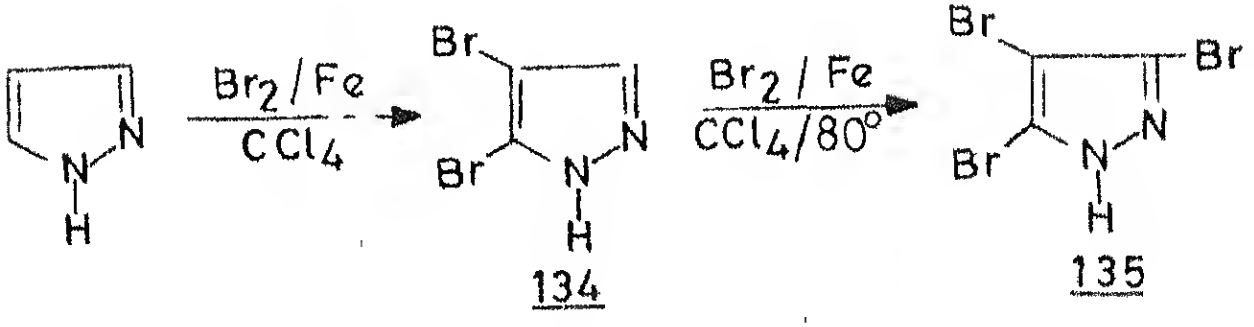
Chlorination of pyrazoles[83-84] in neutral or weakly acid media leads to 4-chloro pyrazoles, successful chlorinating agents are sulphuryl chloride[83] or phosphorous pentachloride[85] in neutral medium, at low temperatures.

Huttel, Schaefer and Welzel[86] established that free chlorine in weakly polar solvents reacted with 3-methyl-pyrazole to give 3-methyl-4-chloro-pyrazole. In acetic acid solution, the reaction

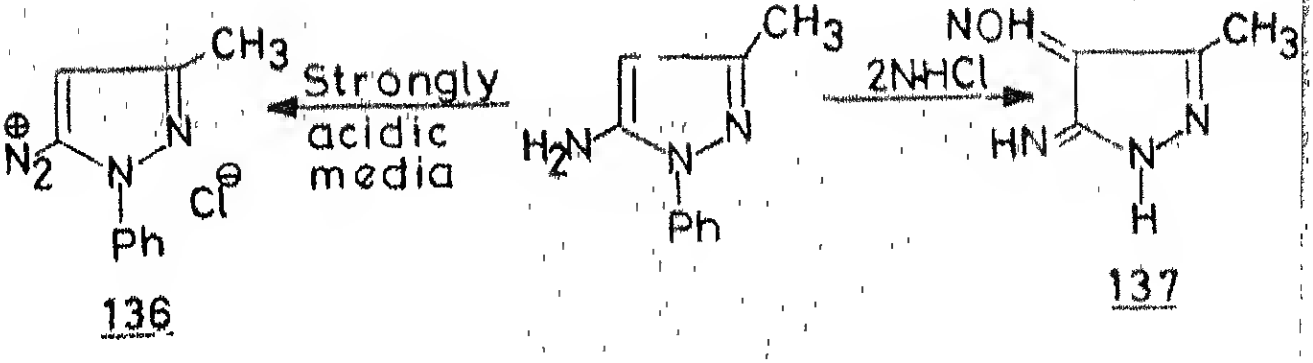
Scheme I.27



Scheme I.28



Scheme I.29



proceeded further to 3-methyl-4,5-dichloro and then 3-trichloro methyl-4,5-dichloro pyrazole (Scheme I.27).

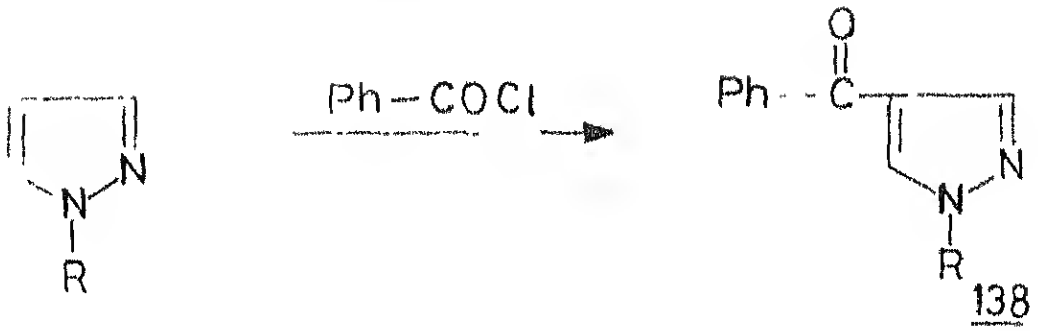
Bromination in the 4th position is the most facile reaction of all pyrazole electrophilic substitution. Bromination in the presence of iron resulted in the introduction of two or three bromine atoms (Scheme I.28). Hypobromous acid and N-bromosuccinimide were also used as the brominating agents.

Direct nitrosation of pyrazoles is accomplished to obtain 4-Nitroso pyrazoles[88] (Scheme I.29). In a strongly acidic medium, the pyrazole nucleus exists as a cation, from which the hydrogen at position-4 cannot be displaced by nitrosation.

Heating N-substituted pyrazoles[89] with benzoyl chloride at 200-230^{o} for some hours, yielded 4-benzoyl pyrazoles in high yields, even in the absence of catalysts (Scheme I.30).

The hydrogen atom of the imino group of pyrazoles is sufficiently active to take part in the Mannich reaction.[90] Pyrazoles unsubstituted on nitrogen, gave rise to dialkyl amino derivatives with formaldehyde and secondary amines (Scheme I.31). Pyrazole ring is particularly resistant to reduction,[91] hydrogen over finely divided nickel, even at 150^{o} and 100 atmospheric pressure. Catalytic reduction[92] of a pyrazole ring unsubstituted on nitrogen, with palladium catalyst in acetic acid at 20^{o}, produced N-phenyl-pyrazolines and then at 80^{o}, it is converted to N-phenyl pyrazolidines.

Scheme 1.30



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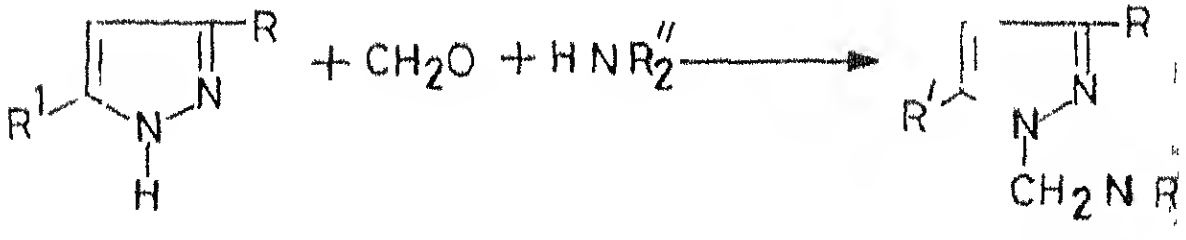
Scheme 1.31



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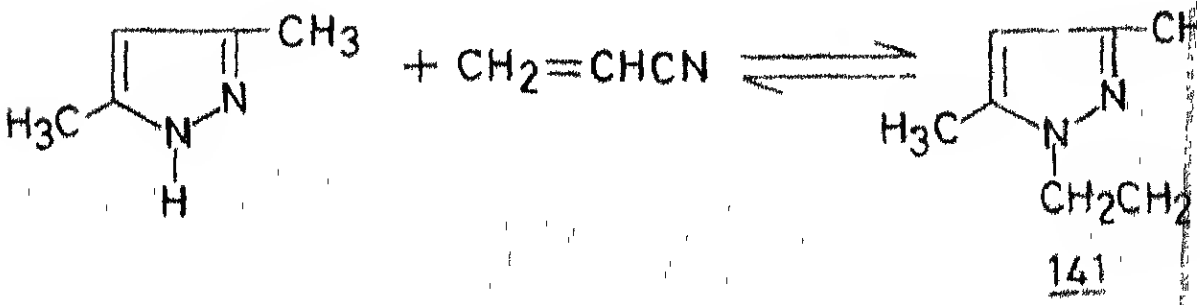
Scheme 1.32



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Pyrazoles undergo Michael addition to α, β-unsaturated acids, and esters,[93] acrylonitrile,[94] maleic anhydride, acetylene dicarboxylic ester,[90] α, β-unsaturated ketones[93] and quinones (Scheme I.32).

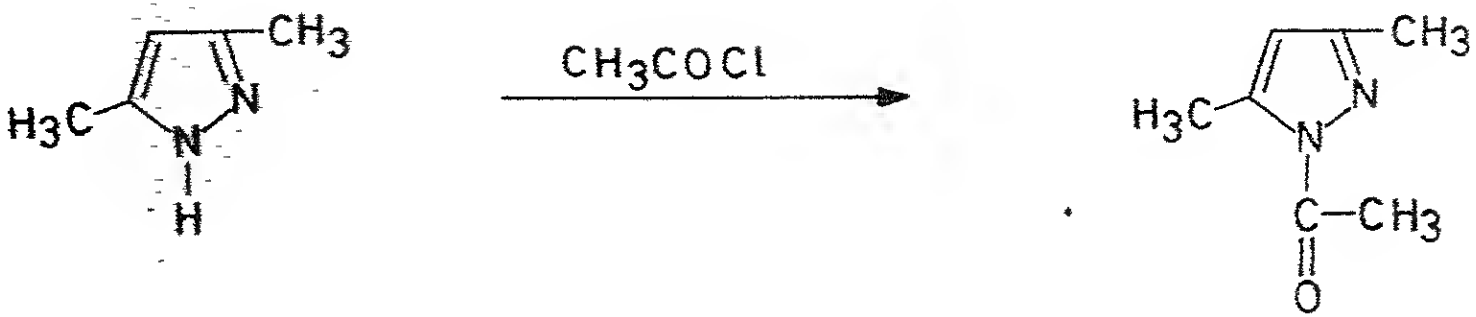
NH group of pyrazole is reported to be acylated with acyl chlorides, anhydrides of aliphatic, aromatic and heterocyclic acids,[95] chloroformic esters, phosgene and other agents to give 1-acyl derivatives (Scheme I.33). Alkylation of free NH group of pyrazoles proceeds by the action of normal alkylating agents[96] (Scheme I.34). The pyrazole ring is stable to oxidation.[97] Various alkyl pyrazoles were oxidized with permanganate.

The most outstanding chemical property of 2-pyrazolin-5-ones is the activity of hydrogen atoms at C-4. This position is very reactive, undergoing the characteristic condensations and substitutions of the active methylene group.

The alkylation[98] of 2-pyrazolin-5-ones at C-4 occurs readily with compounds having reactive halogen atoms (Scheme I.35). 2-pyrazolin-5-ones can be readily acylated at C-4 with acid chlorides,[99] esters[100] and anhydrides.[101] Phthalic anhydride reacts with two moles of 2-pyrazolin-5-one (Scheme I.36).

Ethylisoformanilide, alkylates 2-pyrazolin-5-ones producing 4-anilino-methylidyne-2-pyrazolin-5-ones. Similar products have been obtained by Losco and Passerini[102] by reaction of isonitriles with 2-pyrazolin-5-ones (Scheme I.37).

Scheme 1.33



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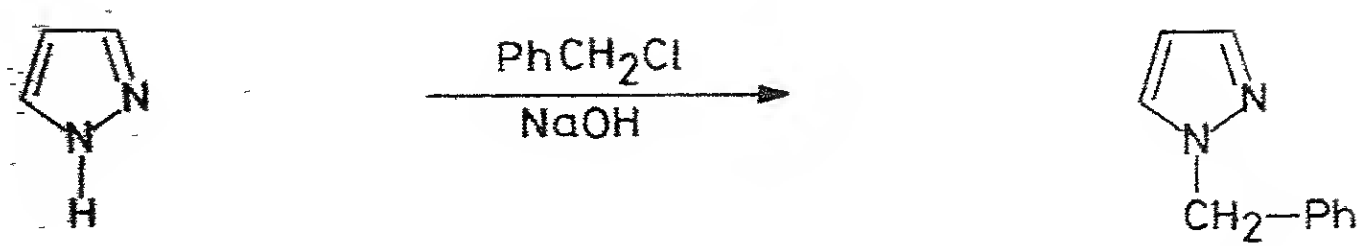
Scheme 1.34



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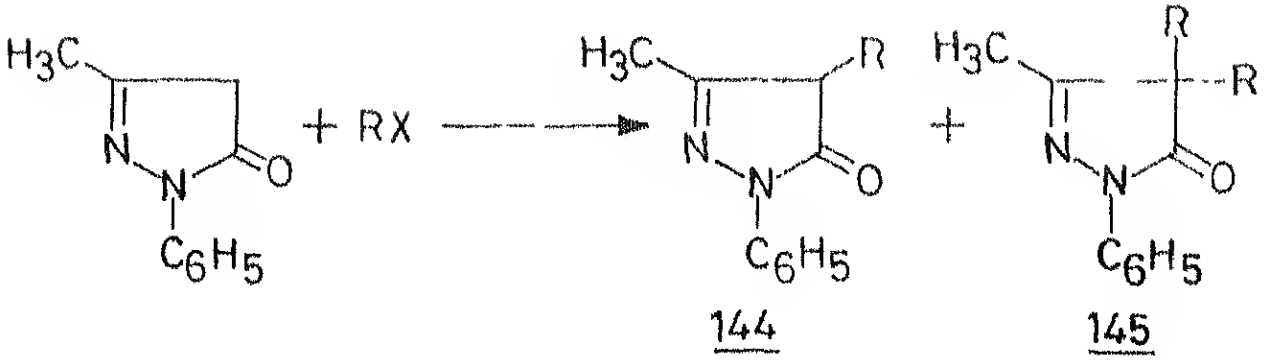
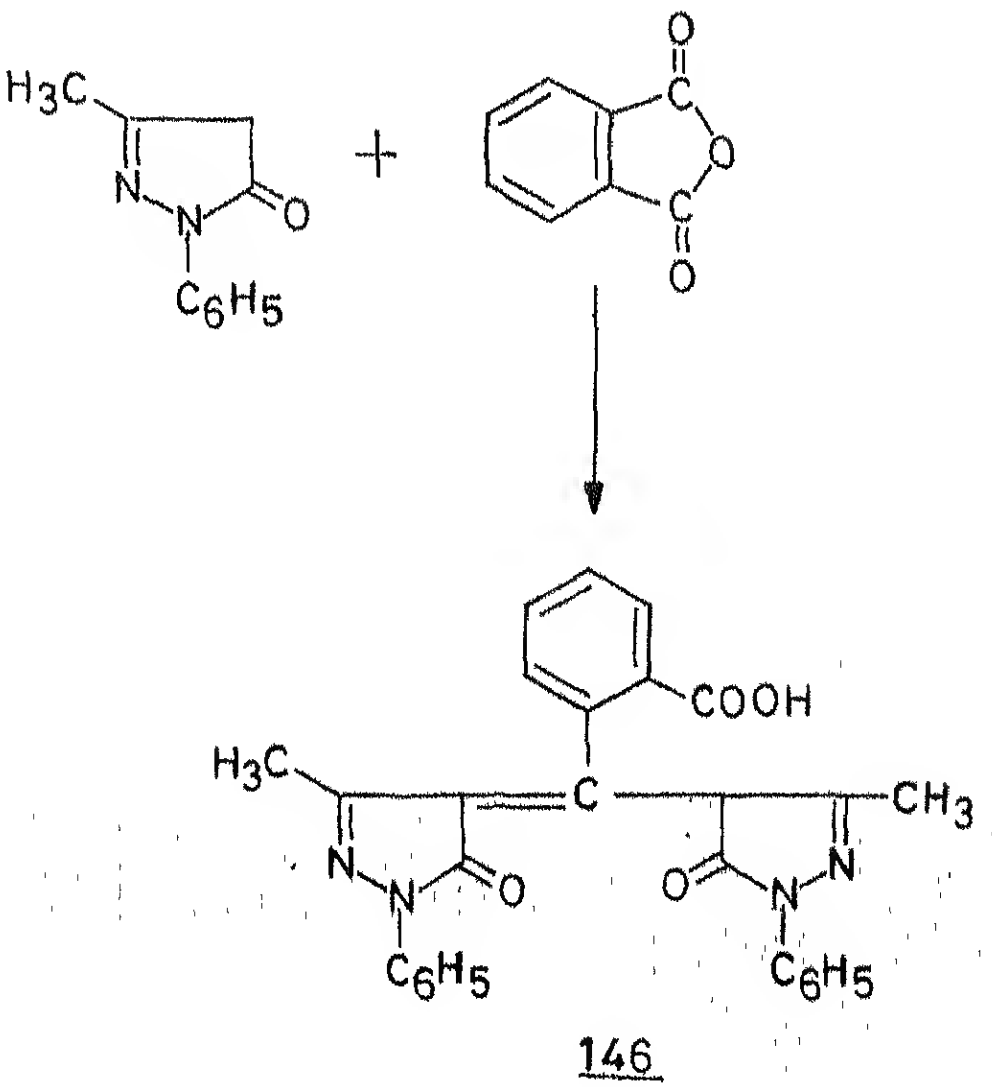
Scheme I.35



Scheme I.36



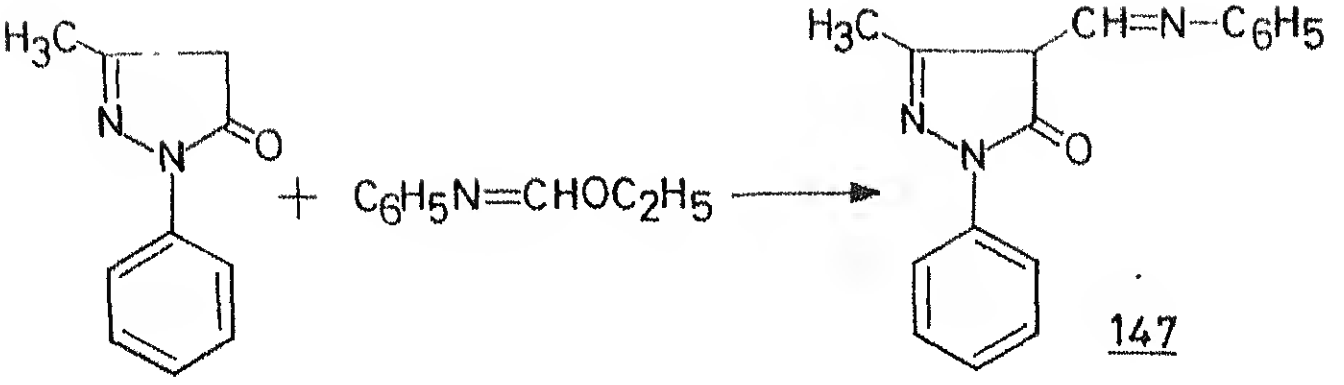
Reaction of 2-pyrazolin-5-ones in reported to occur with phosphorous oxychloride[103] to give 5-chloro-pyrazoles (Scheme I.38). The oxygen of 2-pyrazolin-5-ones is replaced by sulphur when reacted with phosphorous pentasulphide[104] at about 130-150° (Scheme I.39).

5-Imino-2-pyrazolines[105-109] have been prepared by the condensation of β-ketonitriles, β-aldehydo nitriles, β-imino nitriles, α,β-unsaturated trithiones and α,β-acetylenic nitriles with hydrazines as shown in Scheme I.40.

The isoxazole ring system exhibits a characteristic chemical behaviour. Its stability toward agents capable of producing cleavage of the ring is extremely variable. The three positions (3,4 and 5) available for substitution show very different characteristics. The CH group in the 4-position is benzenoid in some respects. The halogens, nitro and sulpho groups can be introduced in this position by electrophilic substitution reactions. Claisen demonstrated that 5-monosubstituted isoxazoles are readily isomerized at ordinary temperature by alkaline alkoxides. Cleavage of the nitrogen-oxygen linkage takes place and the sodium salts of the corresponding cyanoketones are formed.

Nitration[110] of 3,5-dimethyl-isoxazole is reported to occur smoothly on heating with mixed nitric acid and sulphuric acid at 100°, leading to 4-Nitro derivative in 86% yield. Phenyl-isoxazoles are nitrated in the <u>para</u> position of the phenyl nuclei (Scheme I.41).

Scheme I.37



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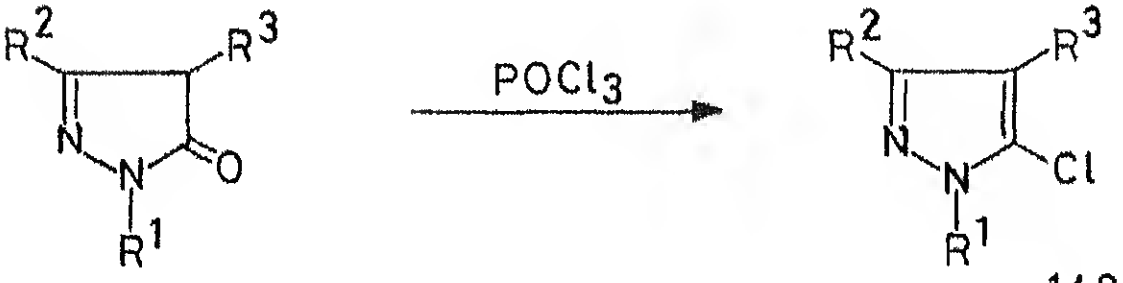
Scheme I.38



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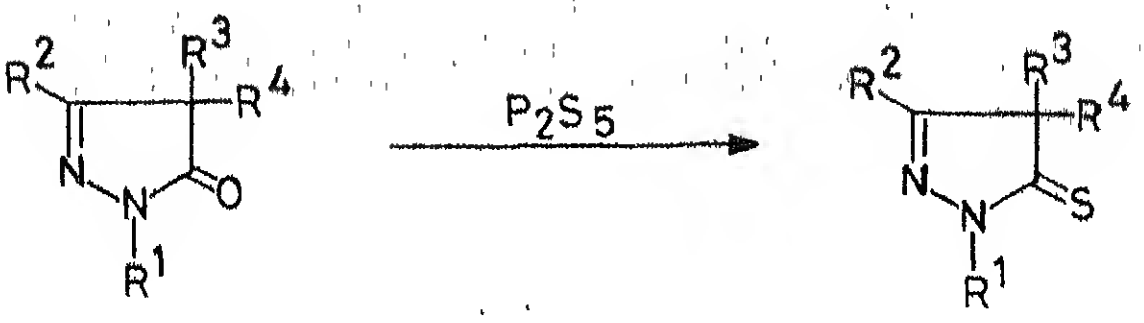
Scheme I.39



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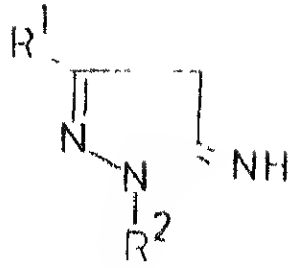
Scheme 40

$R^1CX\,CH_2CN + R^2NHNH_2$ (X = O, NH) ⟶



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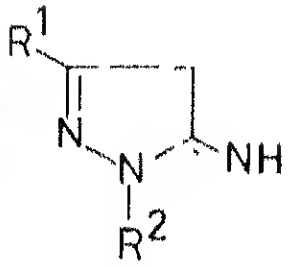
$R^1C{\equiv}CCN + R^2NHNH_2$ ⟶



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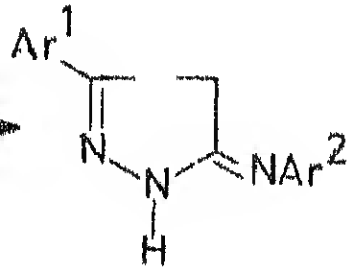
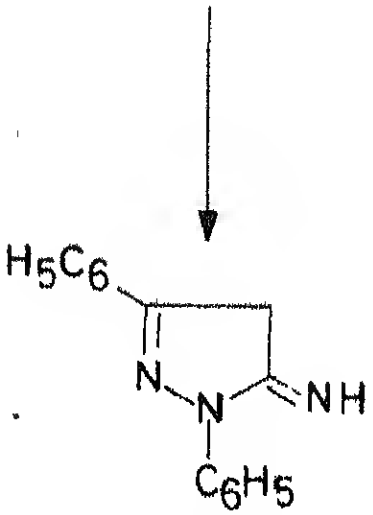
$Ar^1C{\equiv}CCSNH\,Ar^2 + H_2NNH_2$ ⟶



152

$C_6H_5C{=}CH\,CSSS + C_6H_5NHNH_2$



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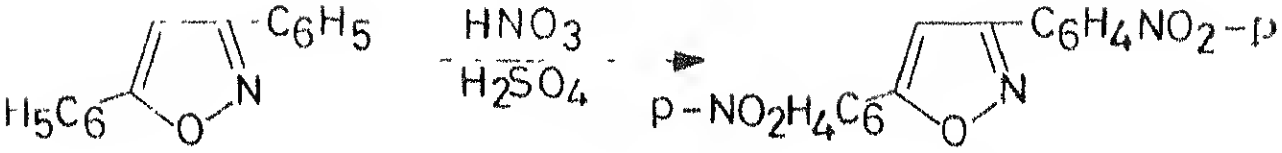
Sulphonation in isoxazoles also takes place of 4th position (Scheme I.42). Isoxazoles apparently behave as nucleophiles in their reactions with diphenyl-cyclopropenone, leading to the formation of pyridones. In a case where 4th position was unsubstituted (R^2=H, R^3=Me), the substituent at 5th position was retained as a 3-acetyl group in the product (Scheme I.43).

Isoxazole nucleus is reported to undergo halogenation[111] in the 4th position, when treated with chlorine/bromine under thermal or photochemical reaction conditions (Scheme I.44). Chloromethylation reaction,[112] well known in the benzene series, has been extended to isoxazoles. This reaction results in the formation of 4-chloromethyl derivatives. To prove the position of the chloromethyl group, these compounds were oxidized to the known isoxazole 4-carboxylic acid (Scheme I.45).

Kochetkov and Khomutova[113] have reported the mercuration of isoxazoles with mercuric acetate. The reaction occurs quite smoothly resulting in 90-100% yield of 4-acetoxy-mercury derivatives. These structureswere proved by converting them to known 4-bromo isoxazoles (Scheme I.46). Cleavage of the isoxazole ring takes place by the action of reducing agents[114] (Scheme I.47). Acetyl acetone imine is obtained by reducing 3,5-dimethyl-isoxazole with sodium in amyl alcohol or moist ether.

The isoxazole ring is found to be stable to many oxidizing agents.[115] In acidic media the ring is not cleaved. Heating isoxazole

Scheme I.41



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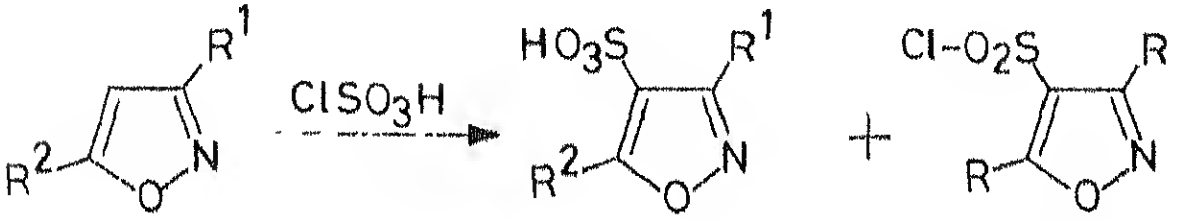
Scheme I.42



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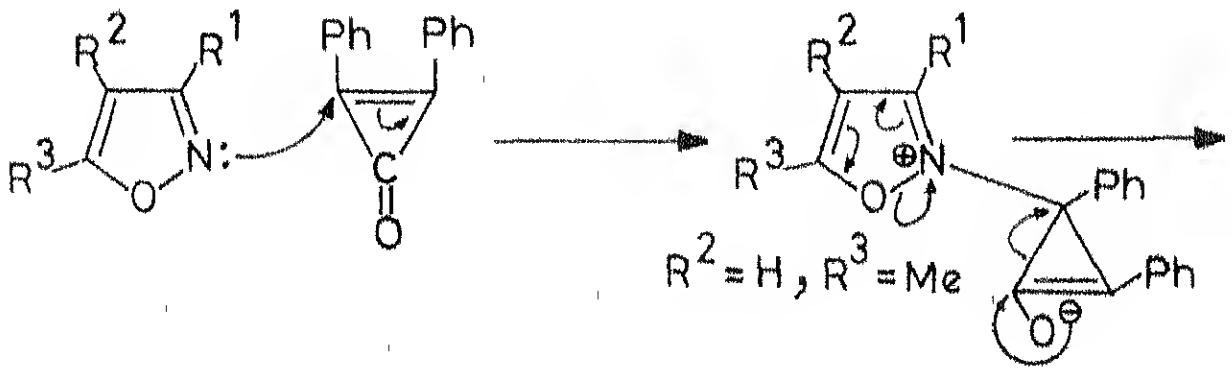
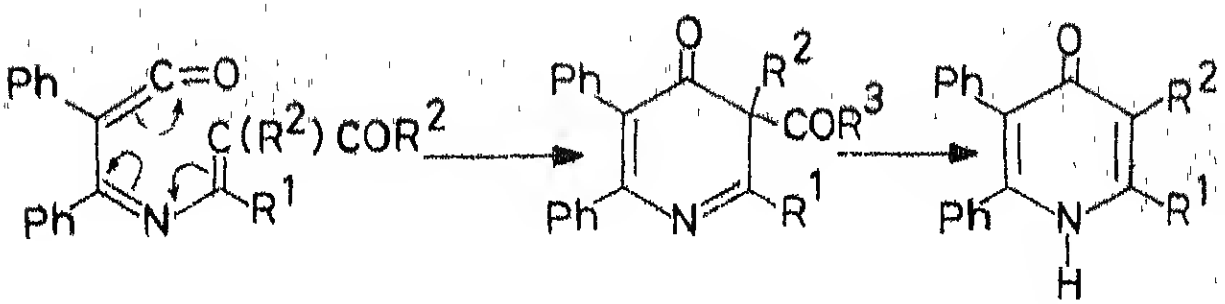
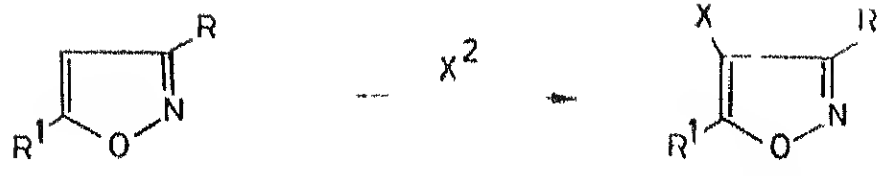
Scheme I.43





157

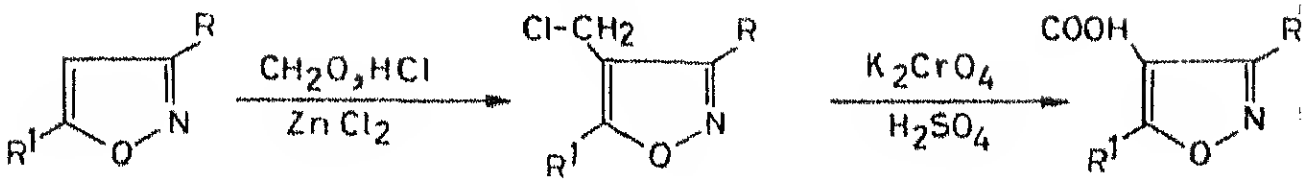
SCHEME I.44



X = Cl, Br, I

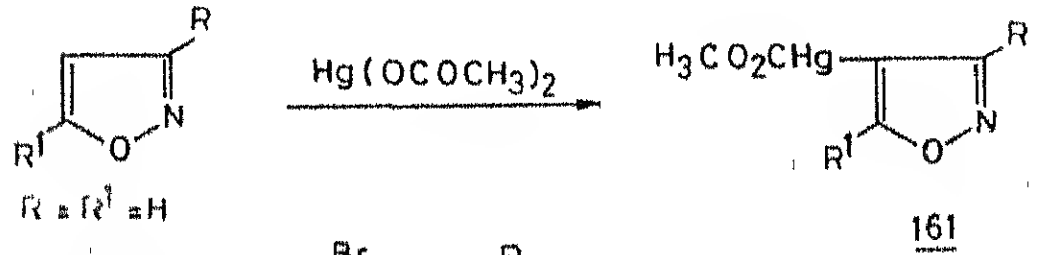
158

SCHEME I.45



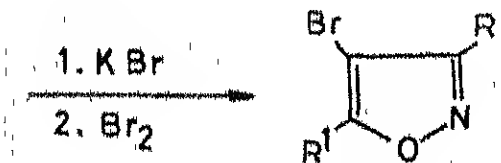
159 160

SCHEME I.46



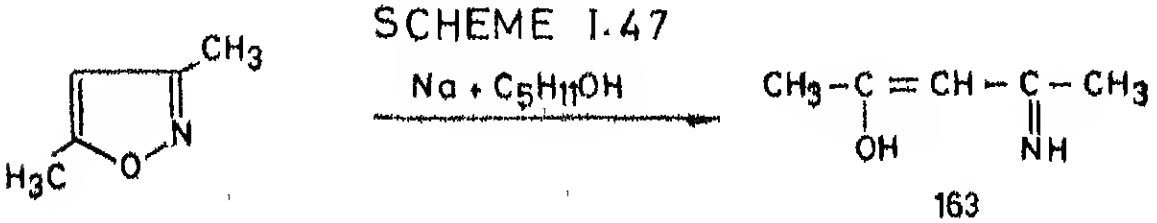
R = R¹ = H

161



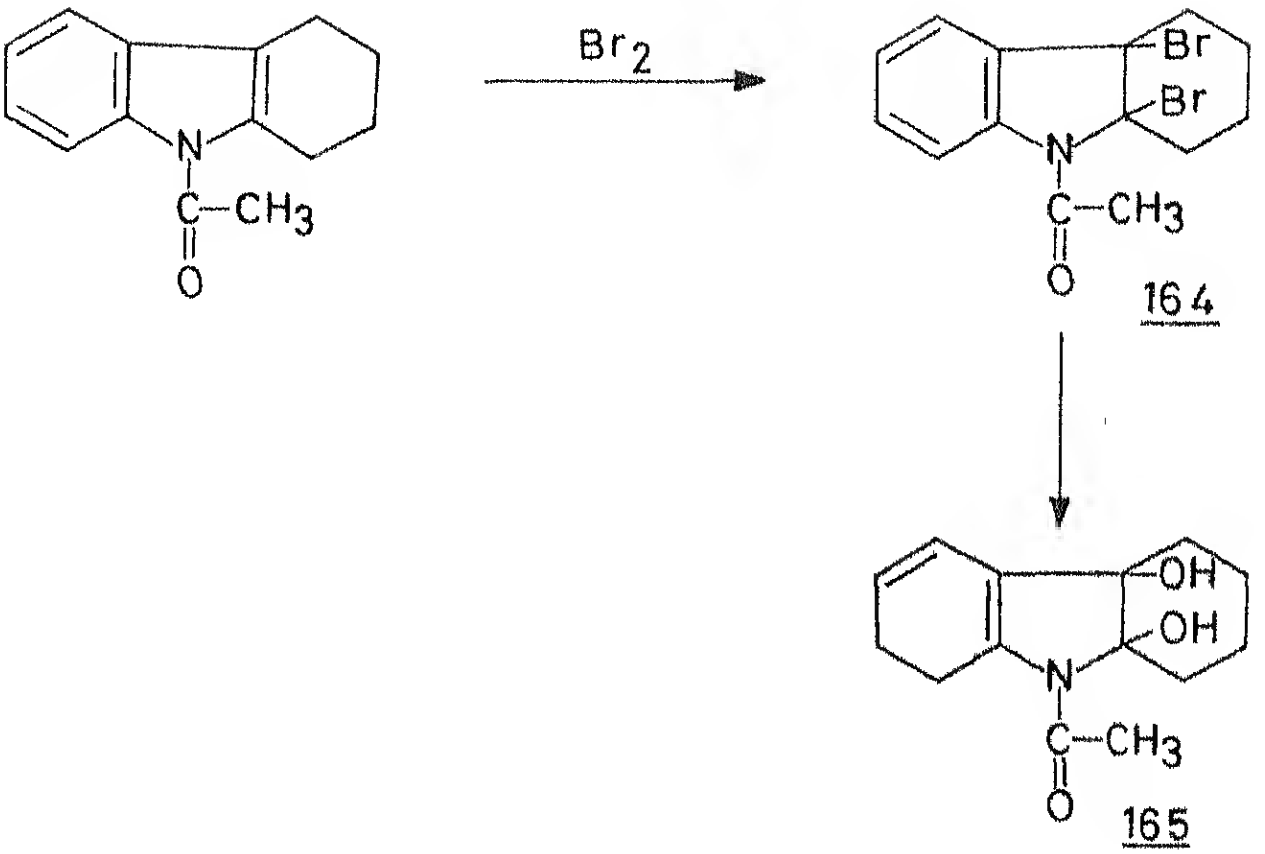
162

SCHEME I.47



163

Schemel.48



Scheme 1.49

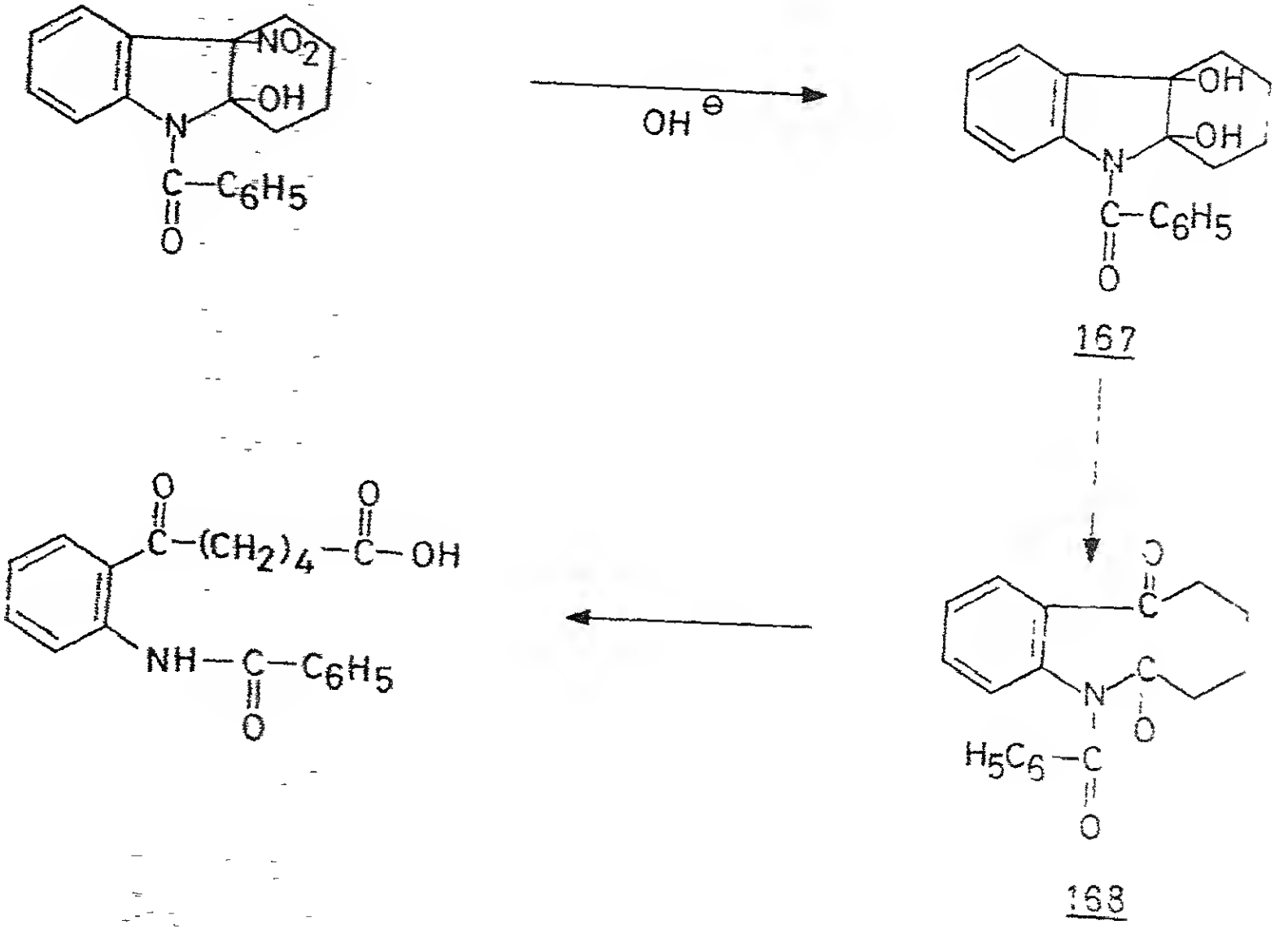
derivatives with aqueous alkaline permanganate leads to a complete degradation of the heterocycle.

Bromination of N-substituted tetrahydrocarbazoles leads to the formation of unstable 10,11-dibromo derivatives which are easily hydrolysed to give the corresponding dihydroxy derivatives[116] (Scheme I.48).

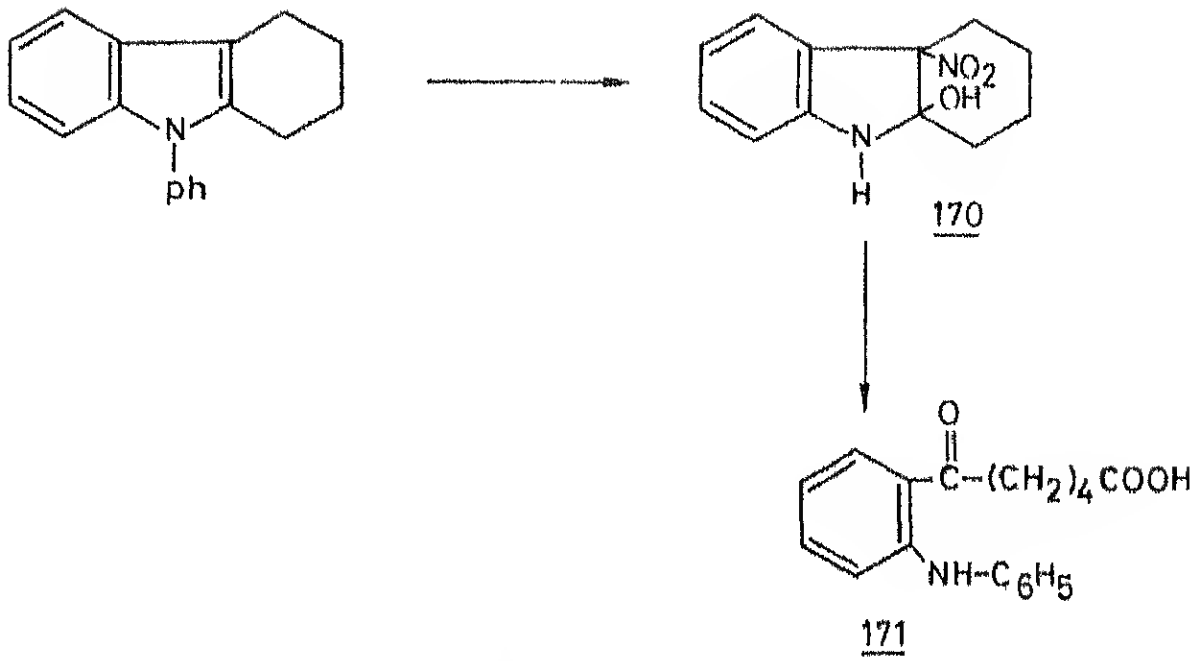
Mononitration of tetrahydrocarbazole and its N-alkyl derivatives with concentrated nitric acid and sulphuric acid gives the 6-Nitro-derivatives,[117] while the N-acyl derivatives nitrate in the 7th position[118]. Under suitable conditions the N-acyl tetrahydro-carbazoles react in a quite different manner, the nitric acid adding at the double bond of the reduced ring[119] (Scheme I.49).

Ring fission occurs on treatment with alkali, leading to the formation of δ-(o-benzyl amino benzoyl) valeric acid (Scheme I.50). N-phenyl derivatives behave like the N-benzoyl derivatives,[120] on treatment of a glacial acetic acid solution of 9-acetyl tetrahydrocarbazole with fuming nitric acid, both substitution and addition take place leading to the formation of 6-Nitro-10,11-dihydroxy-9-acetyl-hexahydrocarbazole[121] (Scheme I.51).

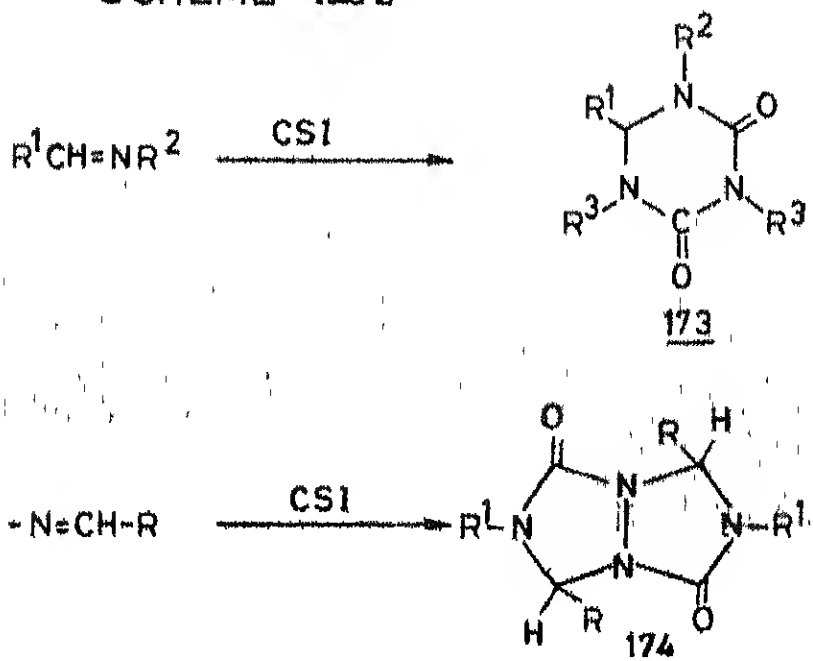
Scheme I.50


NO2
OH
N
C–C6H5
O
OH⊖
OH
OH
N
C–C6H5
O
167
O
C
N
C
O
H5C6–C
O
168
O
C–(CH2)4–C–OH
O
NH–C–C6H5
O

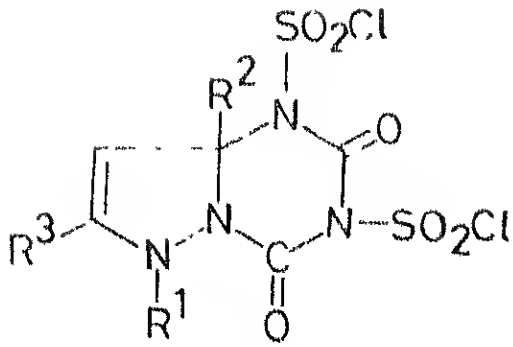
SCHEME.I 51



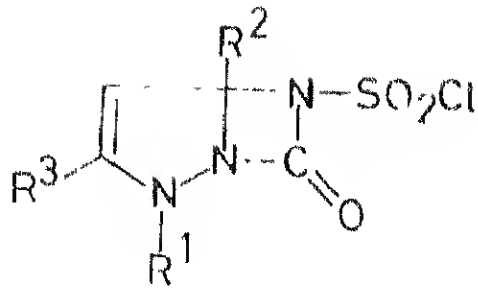
SCHEME I.52



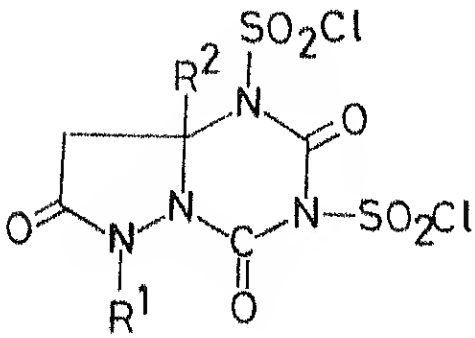
Scheme 1.53



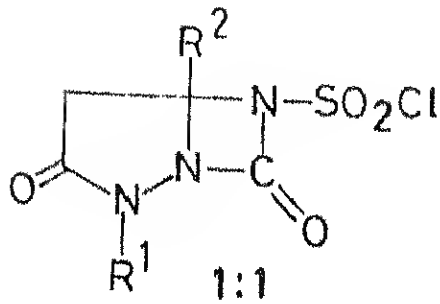
1:2 174 a



174 b

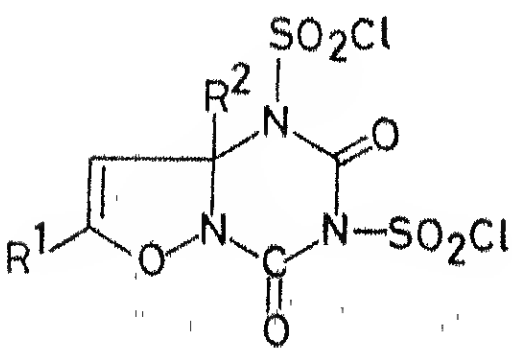


1:2 175 a

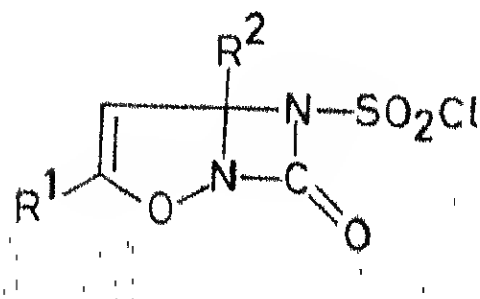


1:1

175 b

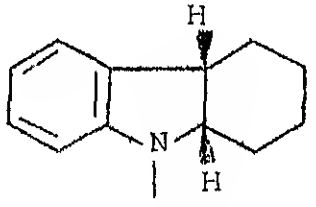


176 a

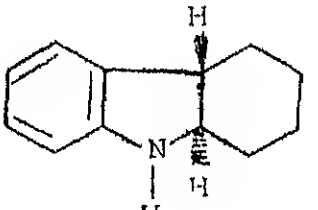


176 b

The hydrogenation of tetrahydrocarbazole gives predominantly the more stable cis form, (vide infra).



172a cis

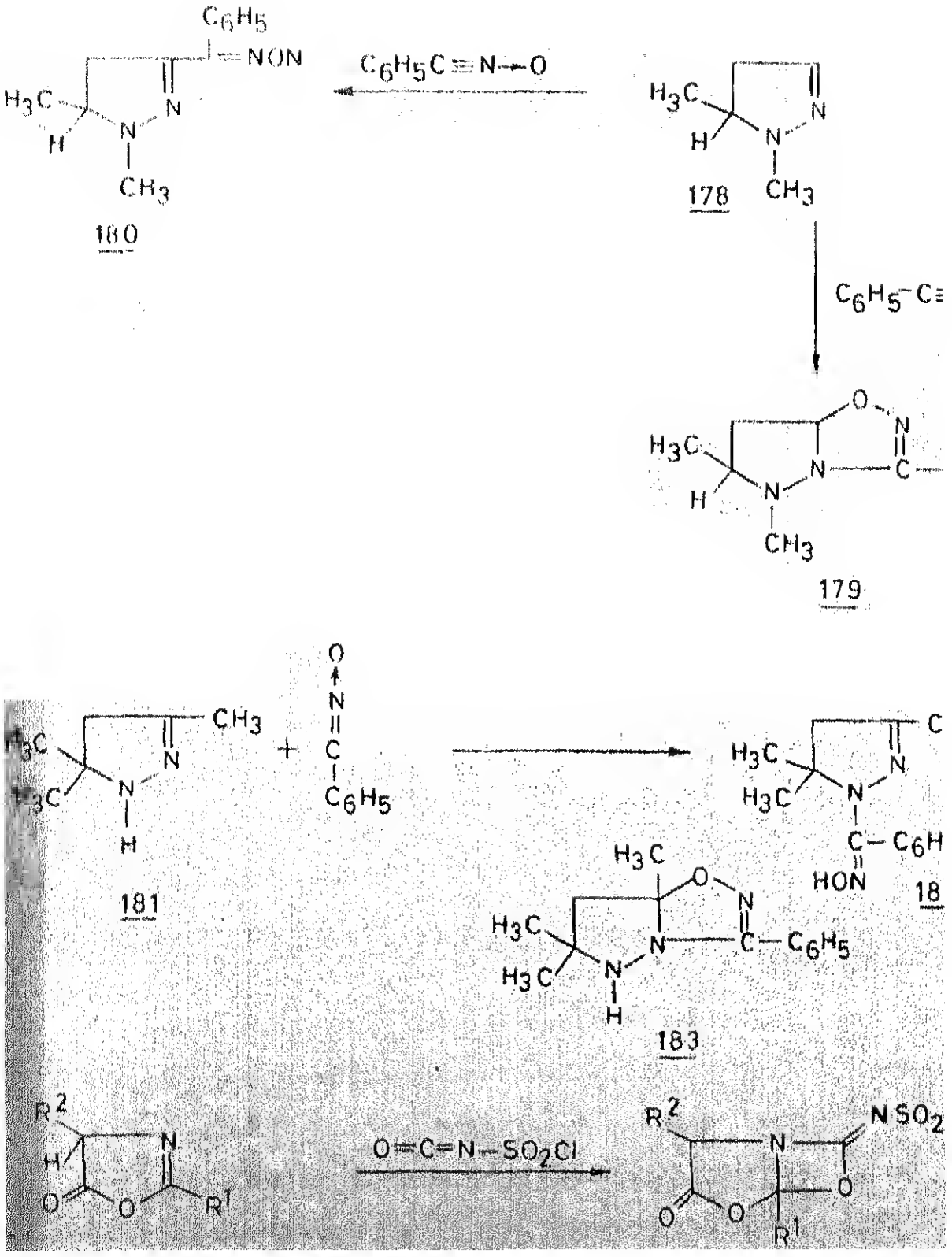


trans 172b

As referred to earlier, CSI (the versatile heterocumulene) is known to undergo reactions with >C=N compounds, to give addition products. Thus, azo-methines add 2 moles of CSI to give triazine-dione in high yields (Scheme I.52).

Under similar conditions pyrazoles, 2-pyrazolin-5-ones and isoxazoles were also expected to give, with chlorosulphonyl isocyanate, either a 1:2 or 1:1 adduct as shown in Scheme I.53. The reaction, however, took an entirely different course. Surprisingly there is no report in the literature about the activity of >C=N bond of pyrazoles, 2-pyrazolin-5-ones and isoxazoles. The >C=N bond in the related systems, viz., 2-pyrazoline and 5-oxazolones, however, have been shown to have a dipolarophilic activity in its reaction with benzonitrile (193) oxide and CSI (183) respectively. (vide Scheme I.54).

SCHEME 1.54


C6H5
NON
H3C
N
H
N
CH3
180
C6H5C≡N→O
178
C6H5-C≡
O
N
C
179
181
18
183
R2
R1
O=C=N-SO2Cl
NSO2

I.3 RESULTS AND DISCUSSION

Reaction of 3,5-dimethyl-pyrazole (184a), 3-methyl-5-ethoxy-pyrazole (184b) with CSI at 0^{o}, took place smoothly, as shown in Scheme I.55. Lone pair of electrons on nitrogen (at position-2) attacks on electrophilic carbon centre of isocyanate moiety, giving rise to a zwitterion, which gets stabilized by the migration of one proton from nitrogen atom at position-1, producing intermediates, 3,5-dimethyl-pyrazol-1-N-chlorosulphonyl carboximide (185a), 3-methyl-5-ethoxy-pyrazol-1-N-chlorosulphonyl carboximide (185b) respectively. On alkaline hydrolysis (185b) yielded 3-methyl-5-ethoxy-pyrazol-1-N-carboximide (186b).

On the basis of elemental analysis, (185a) corresponded to the molecular formula, $C_6H_8N_3ClO_3S$. It gave molecular ion peak at 237 in the mass spectrum. It exhibited IR absorption bands at cm^{-1}, 3115(ν_{NH}), 1695($\nu_{C=O}$), 1150, 1345(ν_{SO_2}), indicating the presence of $-\overset{O}{\overset{\|}{C}}-NHSO_2Cl$ group. It displayed PMR signals at δ 2.13(s, 6H, CH_3), 5.7(s, 1H, CH), 14.0(b, 1H, NH), exchangeable with D_2O. It was identified as 3,5-dimethyl pyrazol-1-N-chlorosulphonyl carboximide (185a). On the basis of elemental analysis (185b) corresponded to molecular formula $C_7H_{10}ClN_3O_4S$. Mass spectrum showed a peak corresponding to m/e, 169($M^+ - SO_2Cl$) (Fig.I.3). It displayed IR absorption maxima at 3290(ν_{NH}), 1700($\nu_{C=O}$) cm^{-1}, 1595($\nu_{C=N}$), 1150, 1340(ν_{SO_2}), showing the presence of $-CONHSO_2Cl$ group (Fig.I.1).

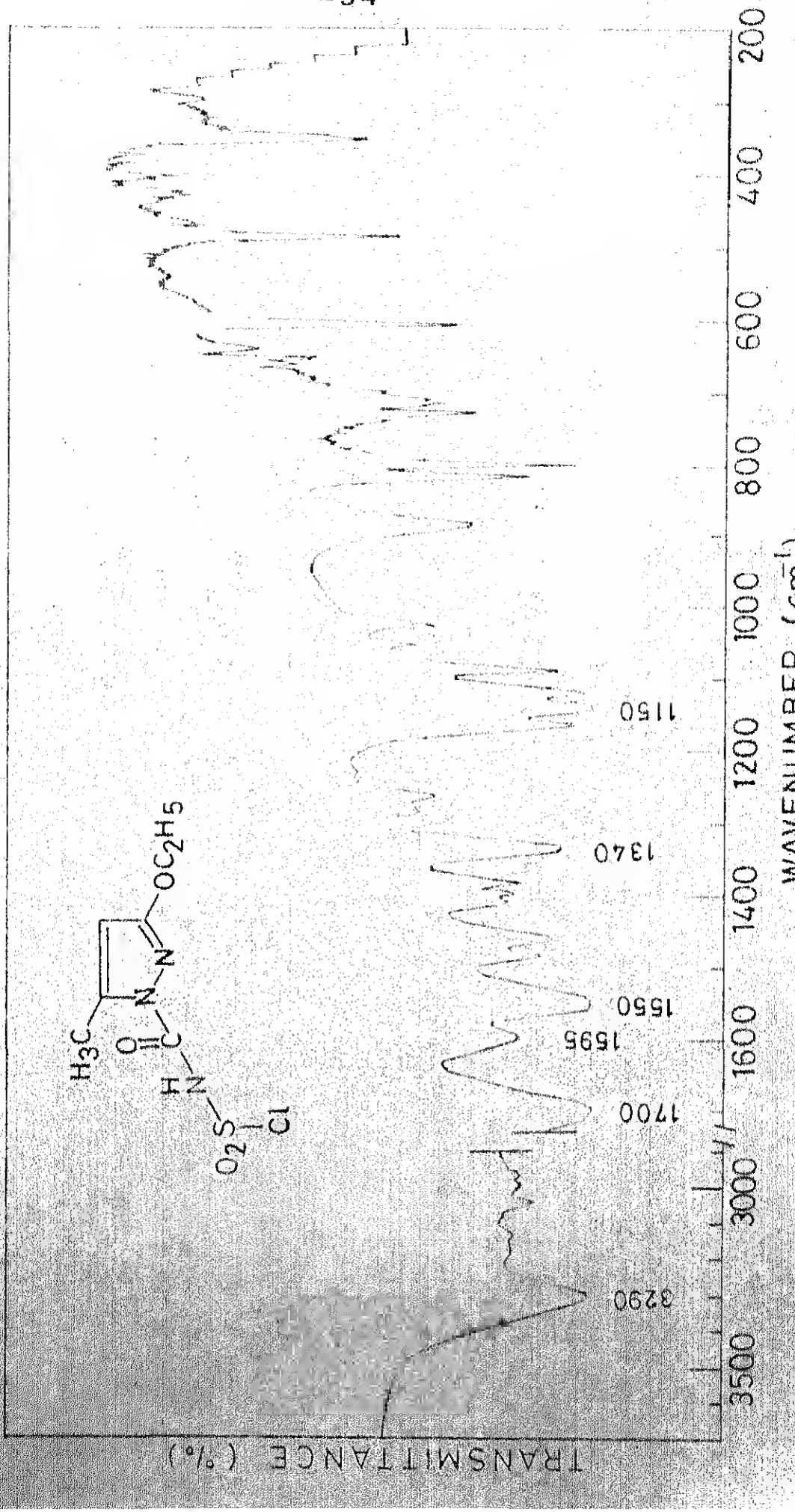
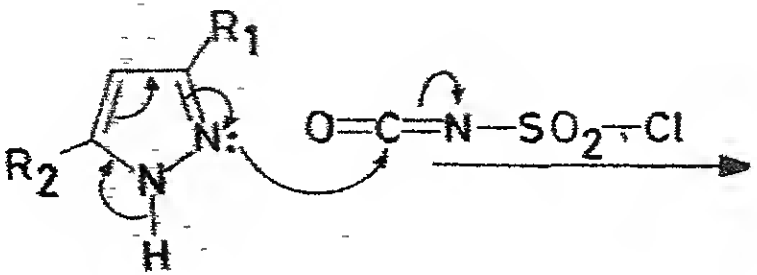
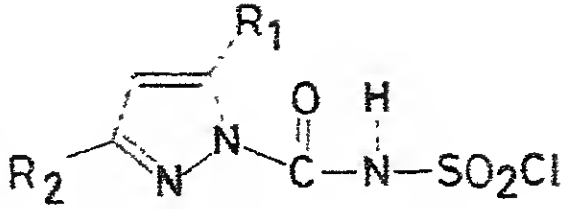


FIG. 1.1 IR SPECTRUM OF 185b.

Scheme I.55

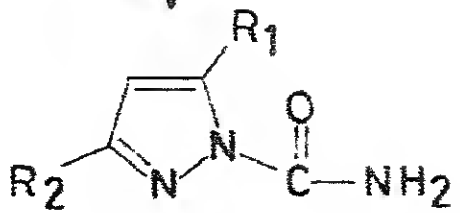


184 a–b



185

Hydrolysis

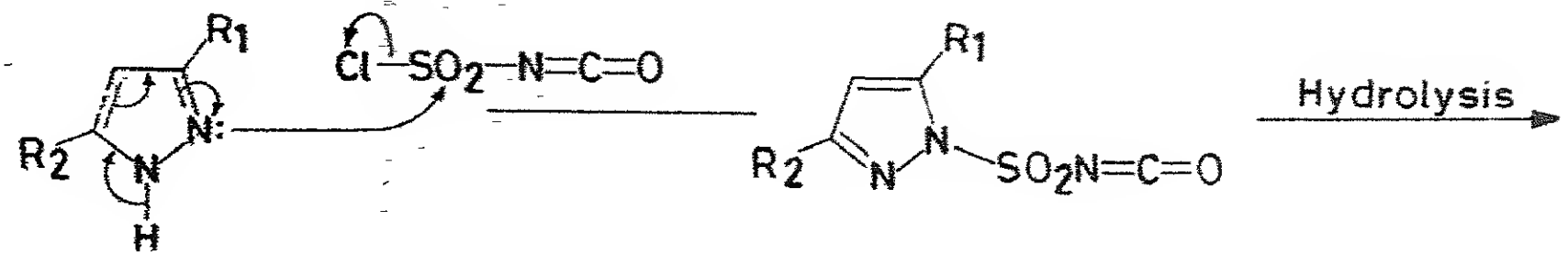


186

a , $R_1 = R_2 = CH_3$

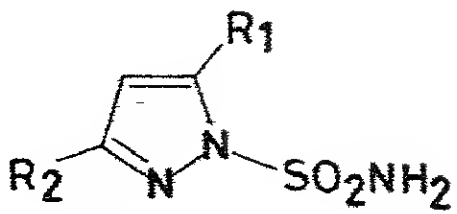
b , $R_1 = CH_3$, $R_2 = OC_2H_5$

Scheme 1.56



184 a,c

187



188

a , $R_1 = R_2 = CH_3$

c , $R_1 = R_2 = H$

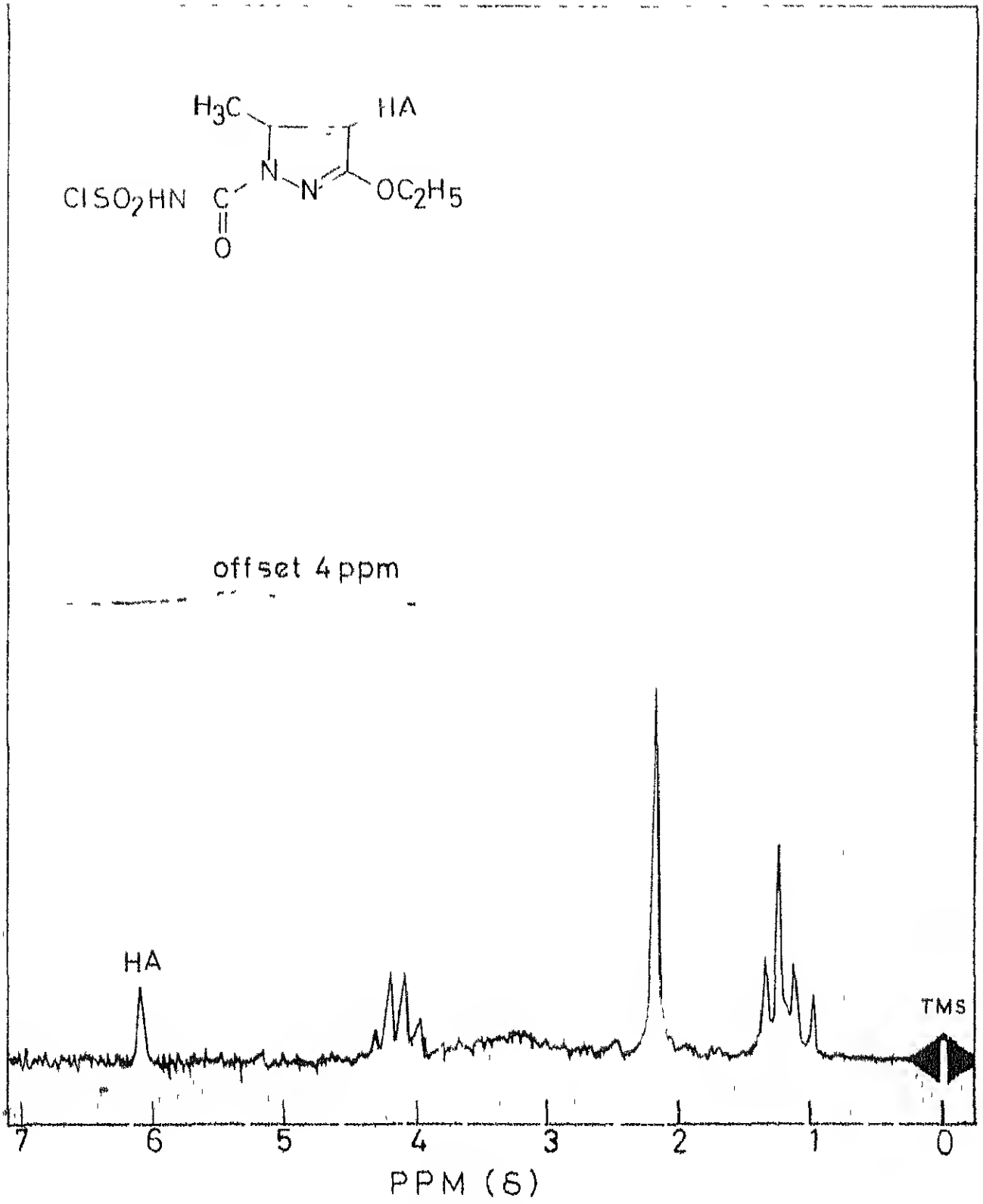


FIG. 1.2 PMR SPECTRUM (90 MHz) OF 185b.

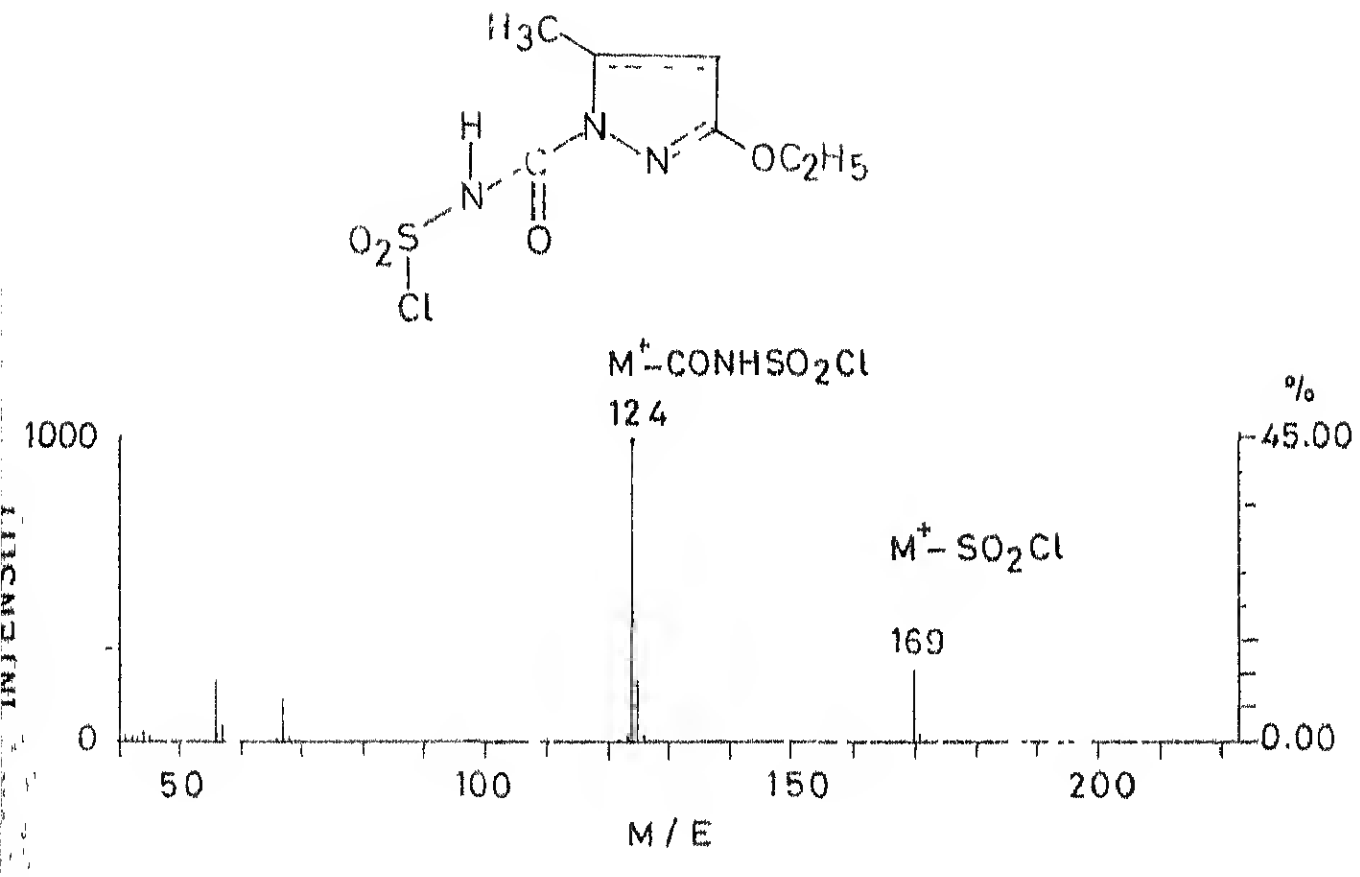


FIG. I.3 MASS SPECTRUM OF 185b.

It was characterized as 3,5--dimethyl-pyrazol-1-N-sulphonamide (188a).

In the foregoing examples, the formation of the products, viz., (188a) and (188c) can be rationalized as follows. (Scheme I.56). The lone pair of electrons on nitrogen atom at position-2 (pyrazole system) attacks on sulphur of the chlorosulphonyl isocyanate, followed by the loss of one proton attached to nitrogen at position-1.

Treatment of 1-[4-nitrophenyl]-3-methyl-5-ethoxy pyrazole with CSI at 0^{o}, was completed within 0.5 hr, yielding a compound which analysed for $C_{13}H_{13}ClN_4O_6S$. It gave molecular ion peak at 388 in the mass spectrum. It showed IR absorption maxima at 3210(ν_{NH}), 1700($\nu_{C=O}$),1170,1350(ν_{SO_2})cm^{-1}.Indicating the presence of $-\overset{O}{\overset{\|}{C}}-NHSO_2Cl$ group. It displayed PMR signals at δ 8.1 (s, 4H, aromatic), 6.4 (b, 1H, NH), exchangeable with D_2O, 1.2 (t, 3H,CH_3), 2.2 (s, 3H), 4.1 (2H)C_2H_5.

It was identified as 1-[4-Nitro phenyl]-3-methyl-5-ethoxy-pyrazol-4-chlorosulphonyl-carboximide (190d). On alkaline hydrolysis 190d yielded a compound which on the basis of elemental analysis corresponded to molecular formula $C_{13}H_{14}N_4O_4$. It gave molecular ion peak at 290 in the mass spectrum. It exhibited IR absorption bands at 3205, 3380(ν_{NH_2}), 1680($\nu_{C=O}$), showing the presence of carboximide group. It exhibited PMR signals at δ 2.2 (s, 3H), 4.1 (d, 2H)C_2H_5, 8.5 (s, 4H, aromatic), 6.2(b, 2H,NH_2),

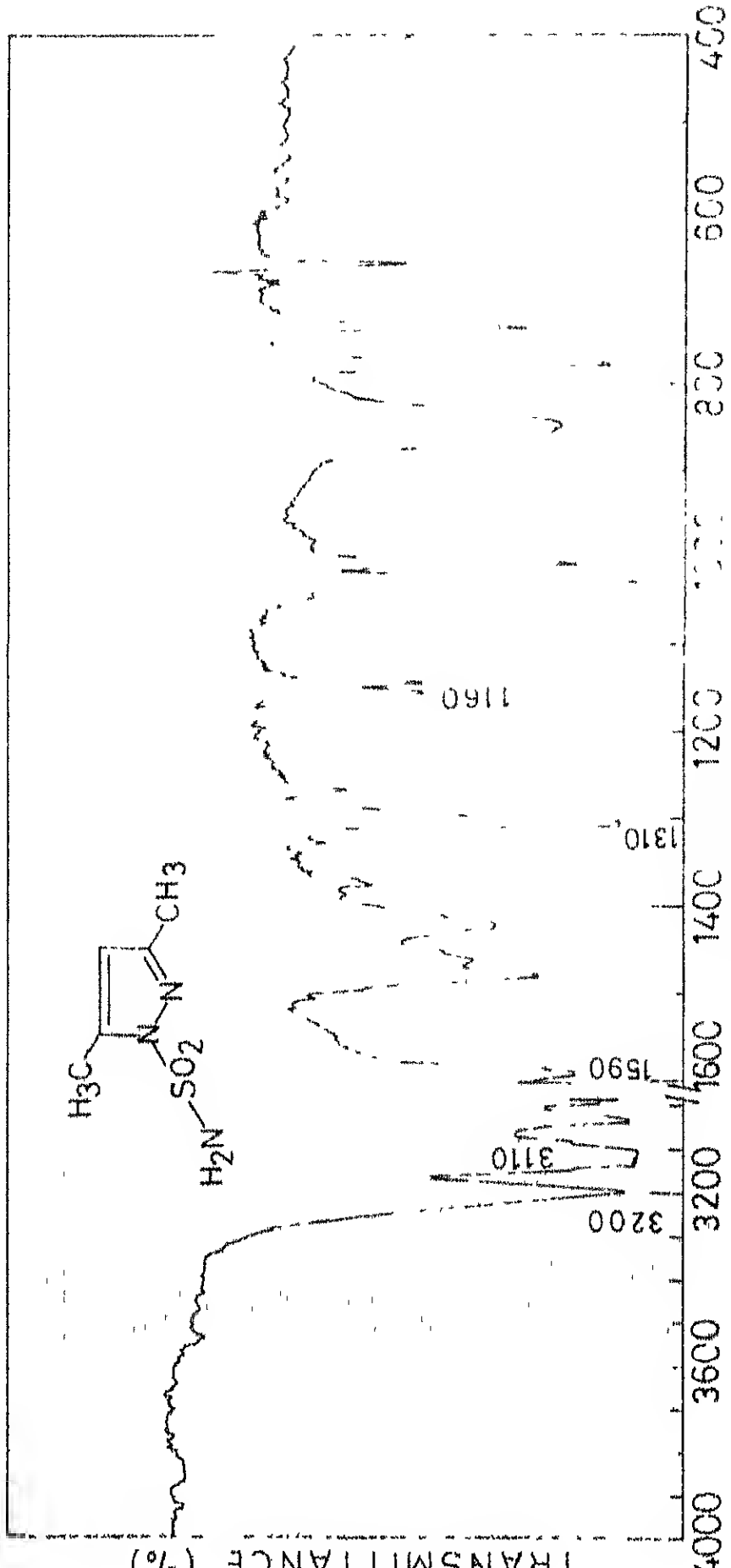


FIG. I.4 IR SPECTRUM OF 188a.

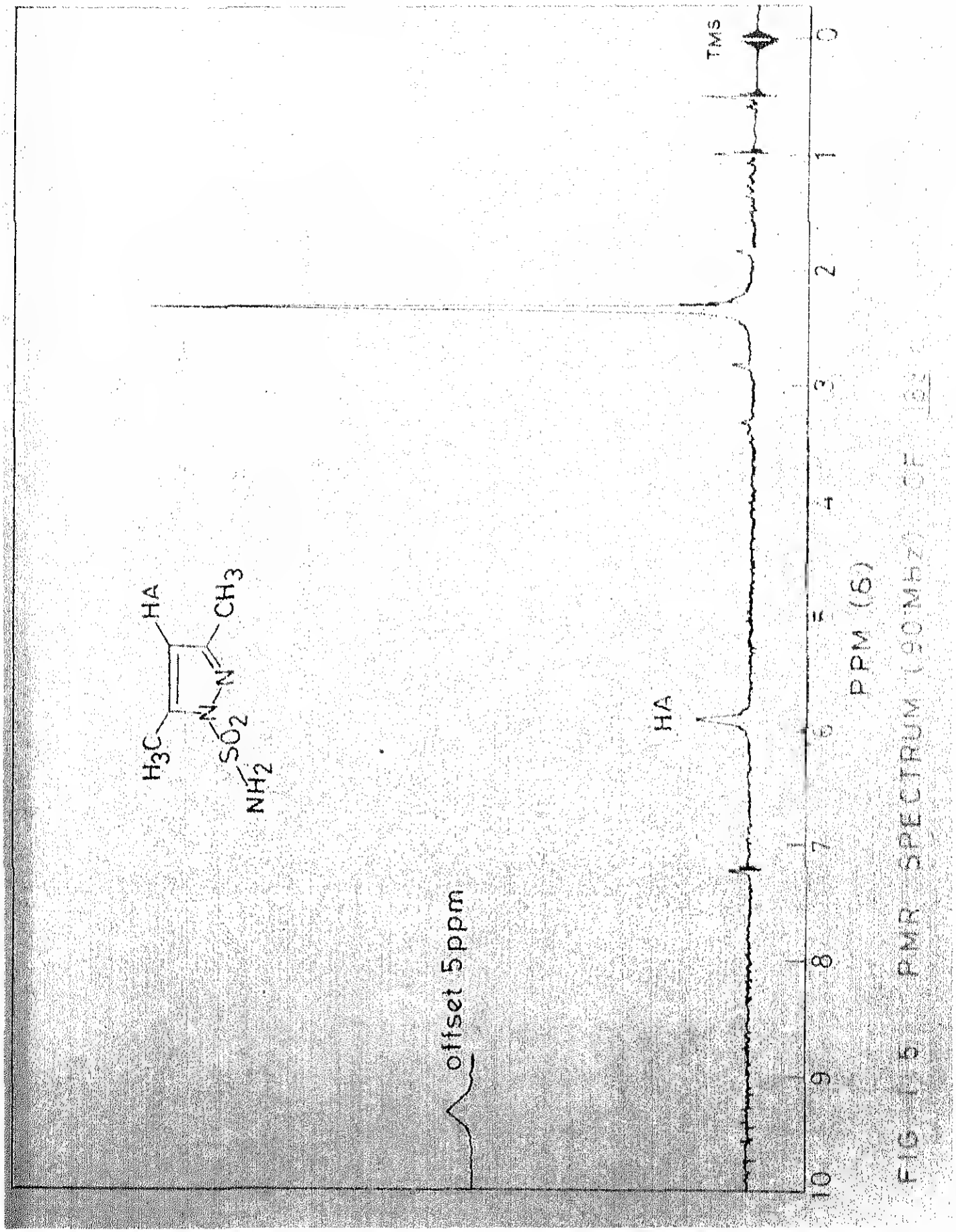
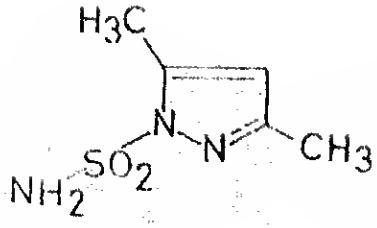


FIG. 15 PMR SPECTRUM (90 MHz, CDCl3)



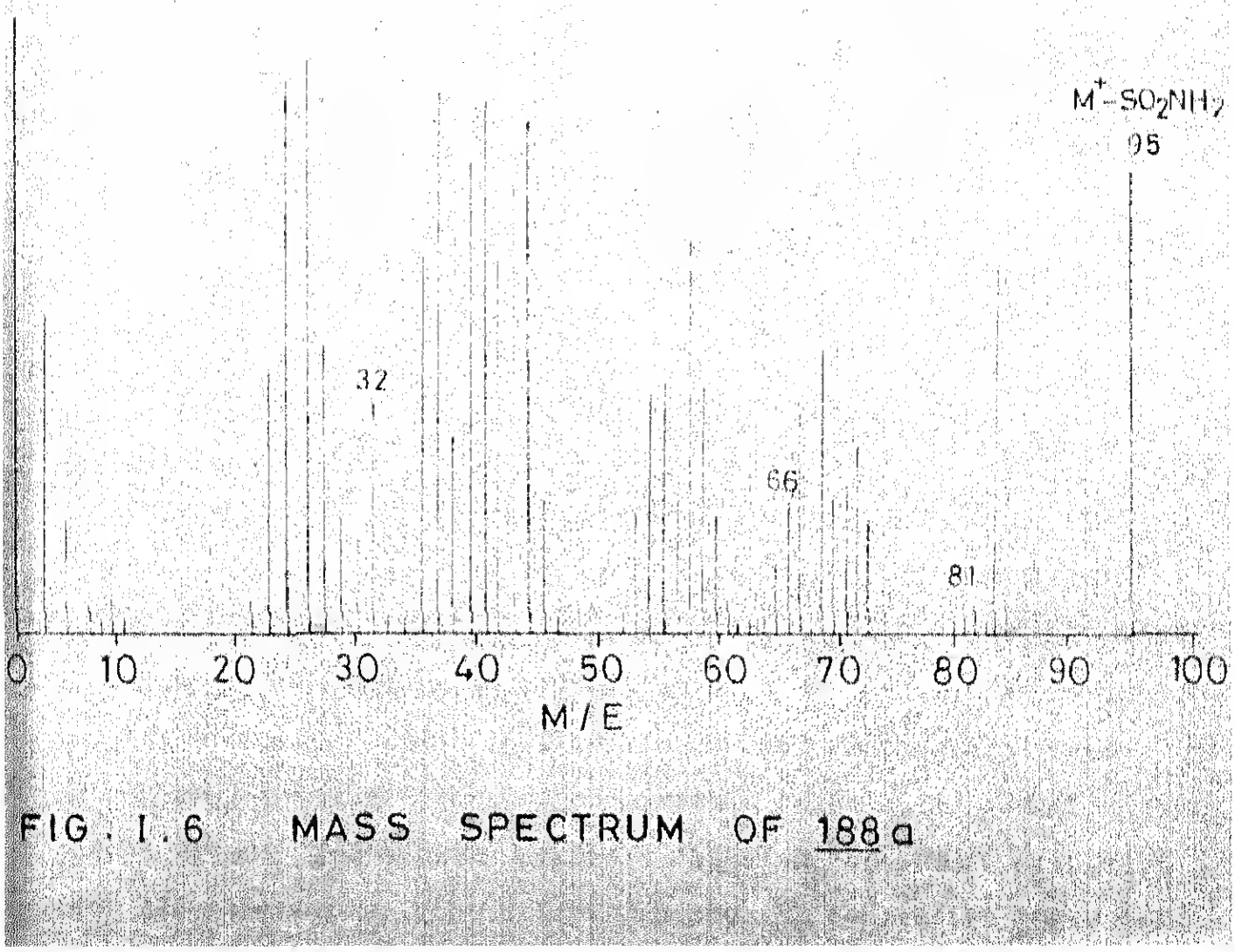
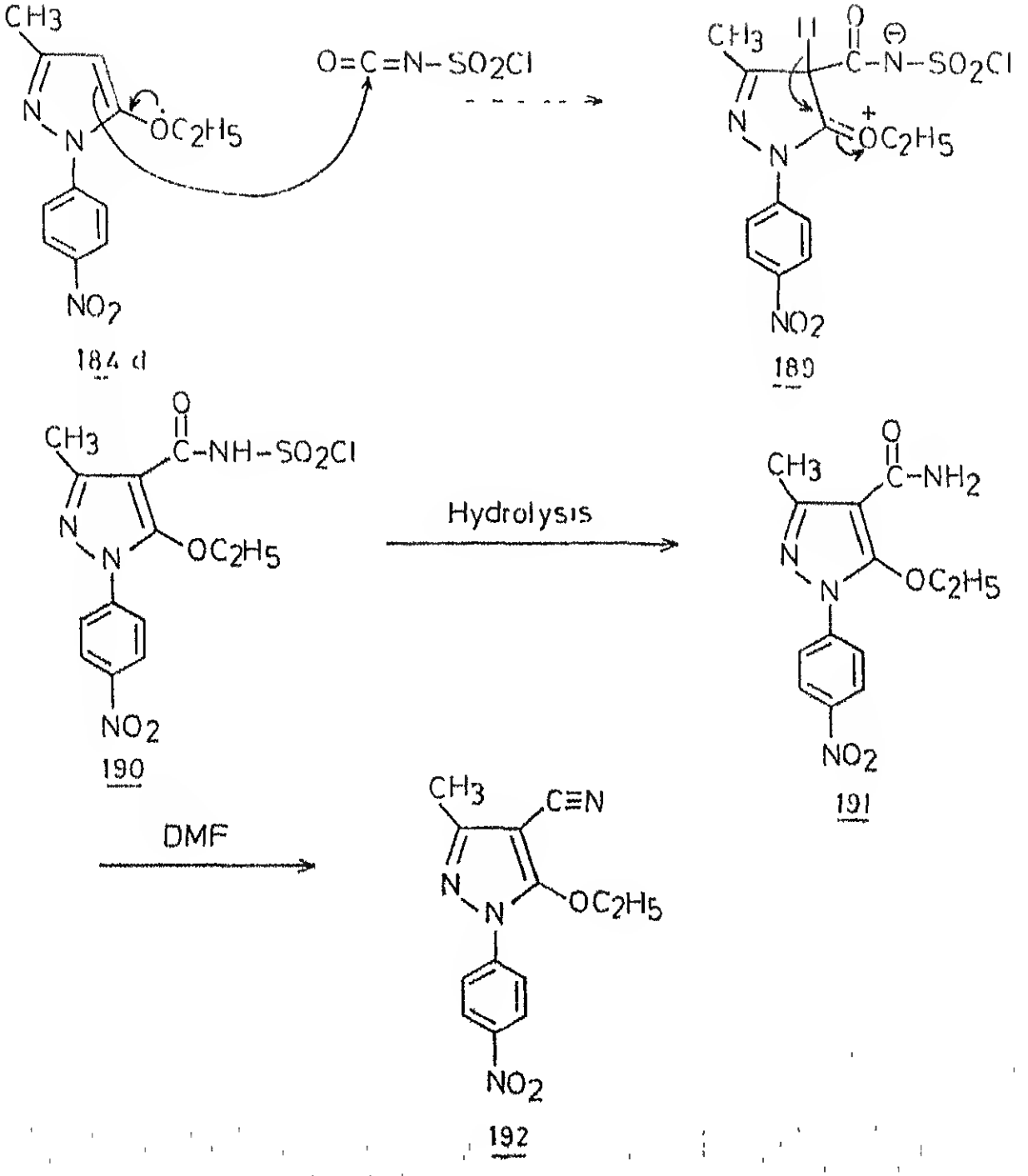


FIG. I.6 MASS SPECTRUM OF 188a

exchangeable with D_2O, 1.2 (t, 3H, CH_3). It was identified as 1-[4-Nitro phenyl]-3-methyl-5-ethoxy pyrazol-4-carboximide (191d). 1-[4-Nitro phenyl]-3-methyl-5-ethoxy pyrazol-4-N-chlorosulphonamide on treatment with DMF produced 1-[4-Nitro phenyl]-3-methyl-5-ethoxy-4-carbonitrilepyrazole. Here the substitution takes place at the most electron rich carbon centre of the pyrazole moiety i.e. 4^{th} position. 192d analysed for $C_{13}H_{12}N_4O_3$ on the basis of elemental analysis. It gave molecular ion peak at 272 in the mass spectrum. It exhibited IR absorption bands at 2135, 2330($\nu_{C\equiv N}$), 1565($\nu_{C=N}$) cm^{-1} (Fig.I.7). It gave PMR signals at 1.1-1.3 (q, 3H, CH_3), 2.2 (s, 3H), 4.12(q,2H)C_2H_5, 7.8-8.3 (M, 4H, aromatic) (Fig.I.8). It was identified as 1-[4-Nitro phenyl]-3-methyl-5-ethoxy-4-carbonitrile (192d).

Treatment of 1-phenyl-3-methyl-5-hydroxy pyrazole (184e) with CSI afforded a compound which on the basis of elemental analysis,analysed for molecular formula $C_{11}H_{11}N_3O_2$. It gave molecular ion peak at 217, in the mass spectrum. It showed IR absorption bands at 1770 ($\nu_{C=O}$), 3120,3360(ν_{NH_2}) cm^{-1}, indicating the presence of urethane >C=O group. It gave PMR signals at δ 7.4-8.4 (M, 5H, aromatic + 2HNH), 6.0 (s, 1H,CH) and was characterized as 1-phenyl-3-methyl-5-carbamato pyrazole (194e). 1-[4-Nitro phenyl]-3-methyl-5-hydroxy pyrazole (184f) on treatment with CSI took place smoothly (Scheme I.58), producing 1-[4-Nitro phenyl]-3-methyl-5-carbamato-pyrazole, which on the basis of elemental analysis corresponded to molecular formula $C_{11}H_{10}N_4O_4$. It gave

SCHEME 157


CH3
O=C=N-SO2Cl
OC2H5
NO2
184 d
189
190
Hydrolysis
191
DMF
C≡N
192

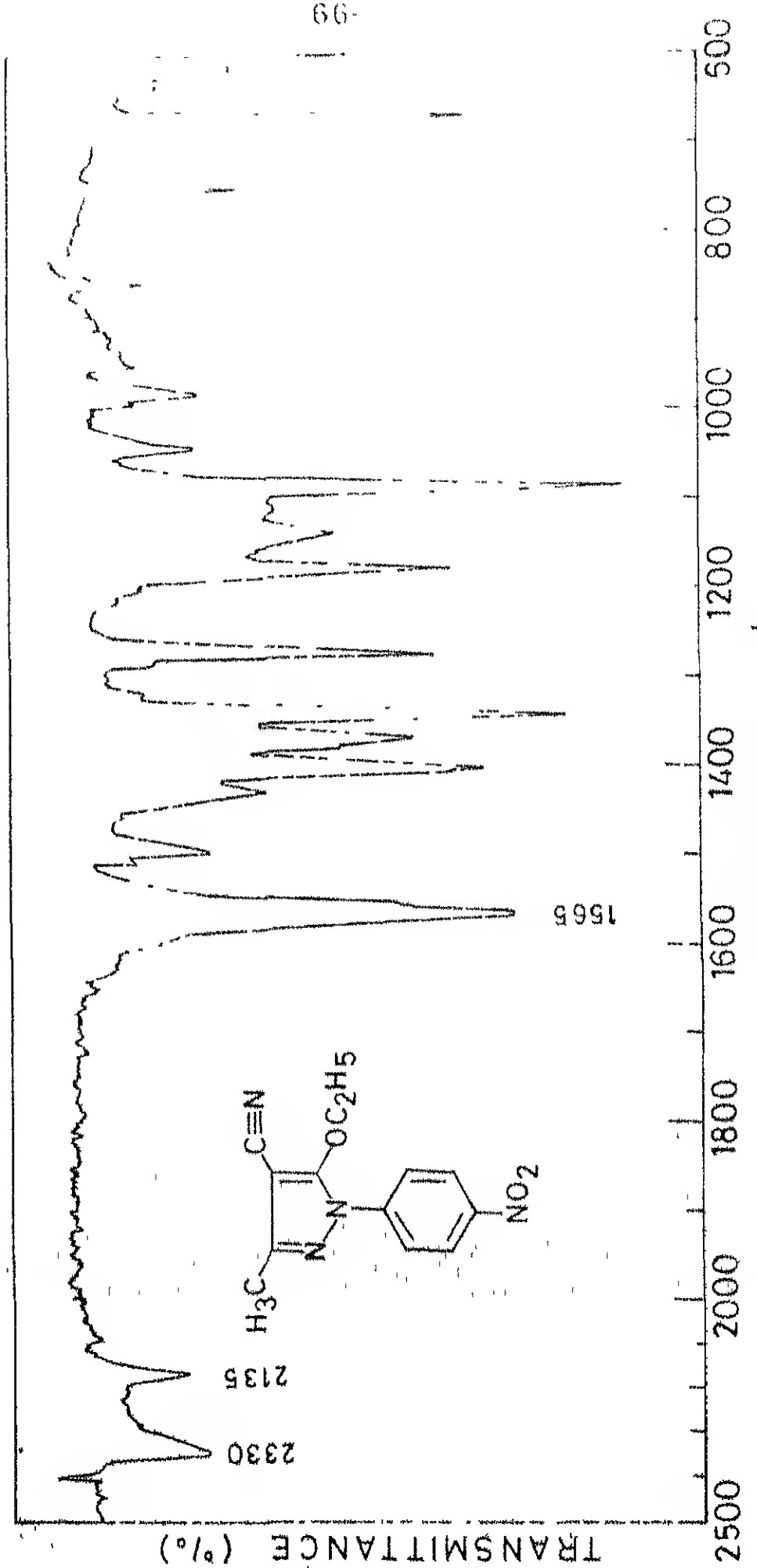


FIG. I.7 IR SPECTRUM OF 192d.

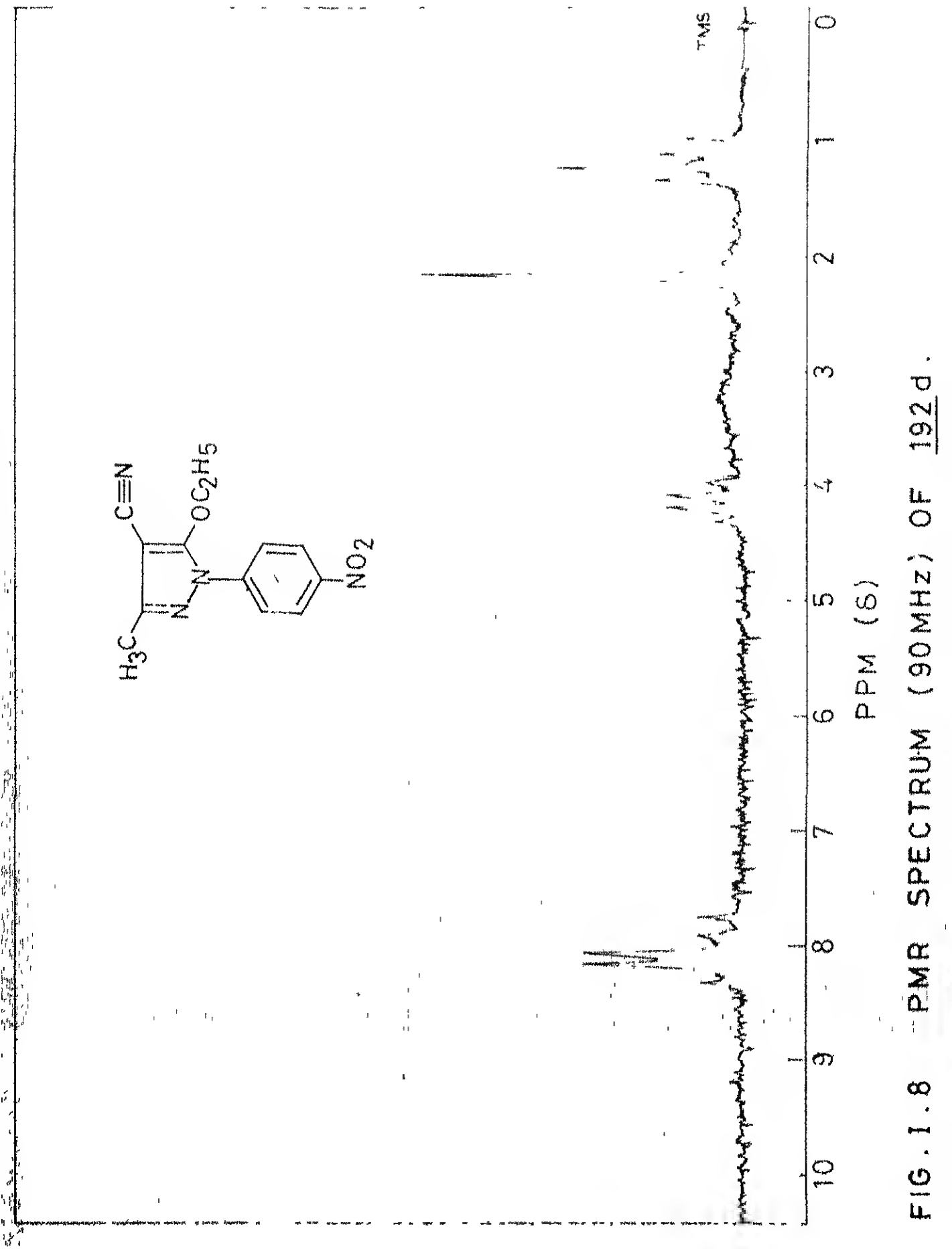


FIG. 1.8 PMR SPECTRUM (90MHz) OF 192d.

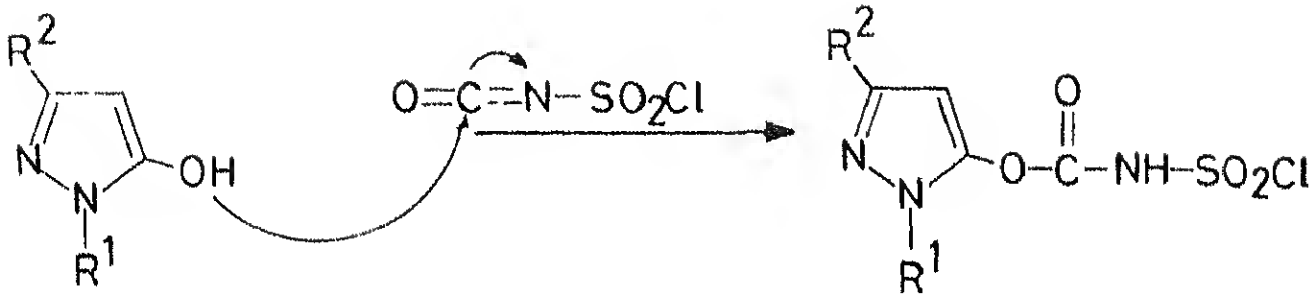
molecular ion peak at 262 in the mass spectrum. It showed IR absorption bands at 1770 ($\nu_{C=O}$), 3120, 3360(ν_{NH_2})cm^{-1}, indicating the presence of urethane ($O-\overset{O}{\overset{\|}{C}}-NH_2$) group. It showed PMR signals at 7.1-8.4(M, 4H, aromatic + 2H,NH), 6.1 (s, 1H, CH), 1.9-2.5(q, 3H, CH_3). It was identified as 1-[4-nitro-phenyl]-3-methyl-5-carbamato-pyrazole (194f).

1-[2,4-dinitro-phenyl]-3-methyl-5-hydroxy -pyrazole(184q) with CSI (Scheme 1.58) yielded a compound which on the basis of elemental analysis corresponded to molecular formula $C_{11}H_9N_5O_6$. Mass spectrum showed a peak corresponding to m/e, 215 ($M^+-(NO_2)_2$) (Fig.I.11). It exhibited IR absorption bands at 1750($\nu_{C=O}$), 3140 3360(ν_{NH_2})cm^{-1}, indicating the presence of urethane group (Fig. I.9).

It gave PMR signals at δ7.2-8.4 (M, 3H, aromatic + 2H,NH), 6.1 (s, 1H,CH), 1.9-2.5 (q, 3H,CH_3) (Fig.I.10). The compound was identified as 1-[2,4-dinitro-phenyl]-3-methyl-5-carbamato-pyrazole (194g).

Reaction of 1-[4-Nitro-phenyl]-3-methyl-2-pyrazolin-5-one (195k), 1-[2,4-dinitro-phenyl]-3-methyl-2-pyrazolin-5-one (1951) with CSI yielded 1-[4-Nitro-phenyl]-3-methyl-2-pyrazolin-5-imide (198k), 1-[2,4-dinitro-phenyl]-3-methyl---2-pyrazolin-5-imide as illustrated in Scheme I.59. Here the CSI underwent (2+2) cycloaddition to)C=O group of 2-pyrazolin-5-one. On the basis of elemental analysis (198k) corresponded to molecular formula $C_{10}H_{10}N_4O_2$. Molecular ion peak appeared at 218 in the mass

Scheme I.58



184 (e-g)

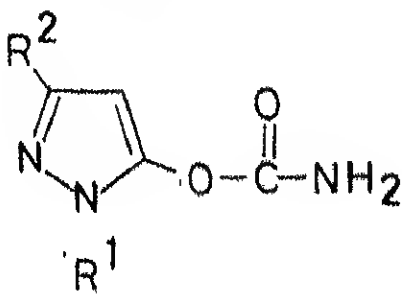
193

$R^1 = C_6H_5$, $R^2 = CH_3$

$R^1 = C_6H_4NO_2$, $R^2 = CH_3$

R^1 $C_6H_3(NO_2)_2$, $R^2 = CH_3$

Hydrolysis



194

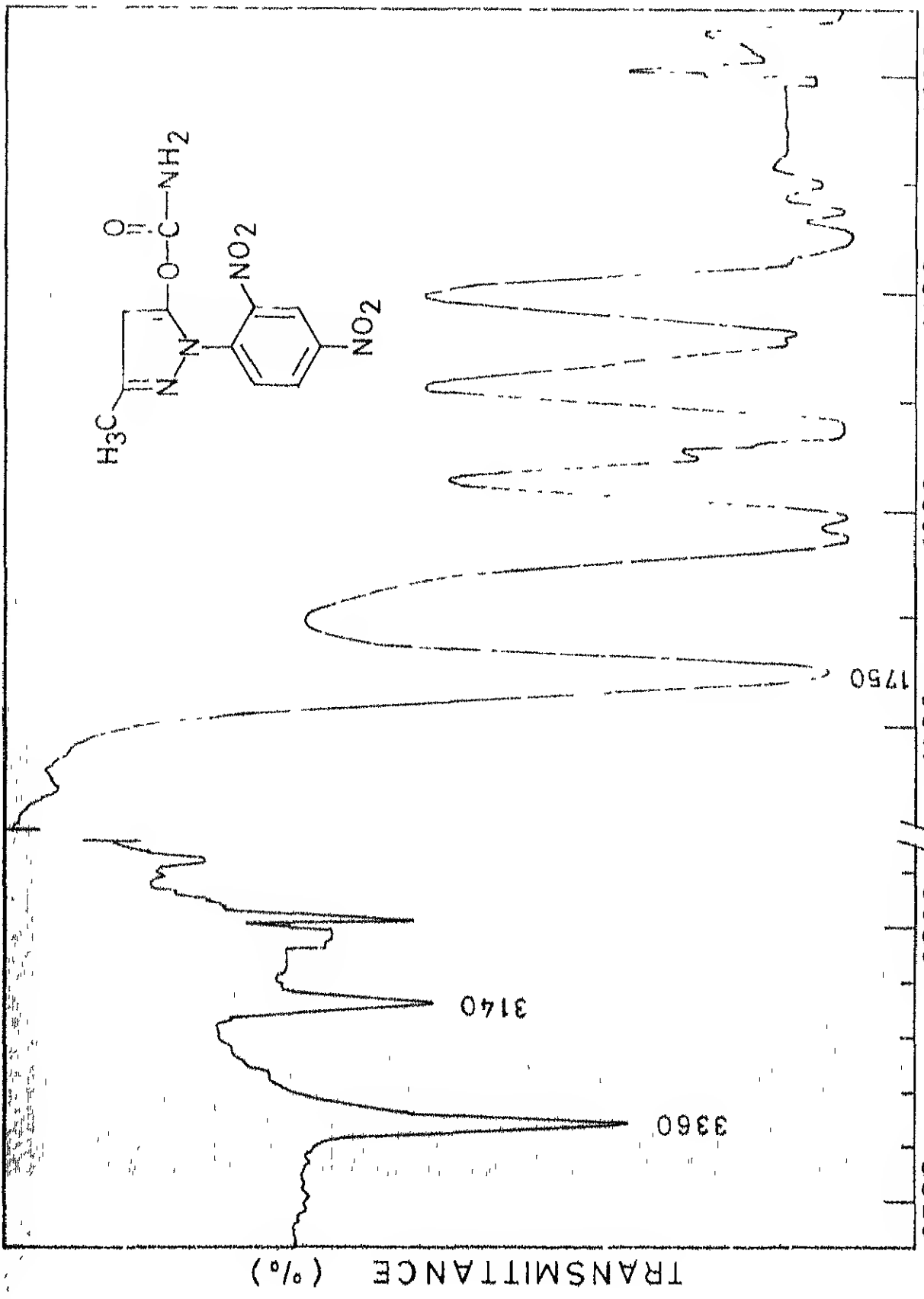


FIG. I. 9 IR SPECTRUM OF 194g.

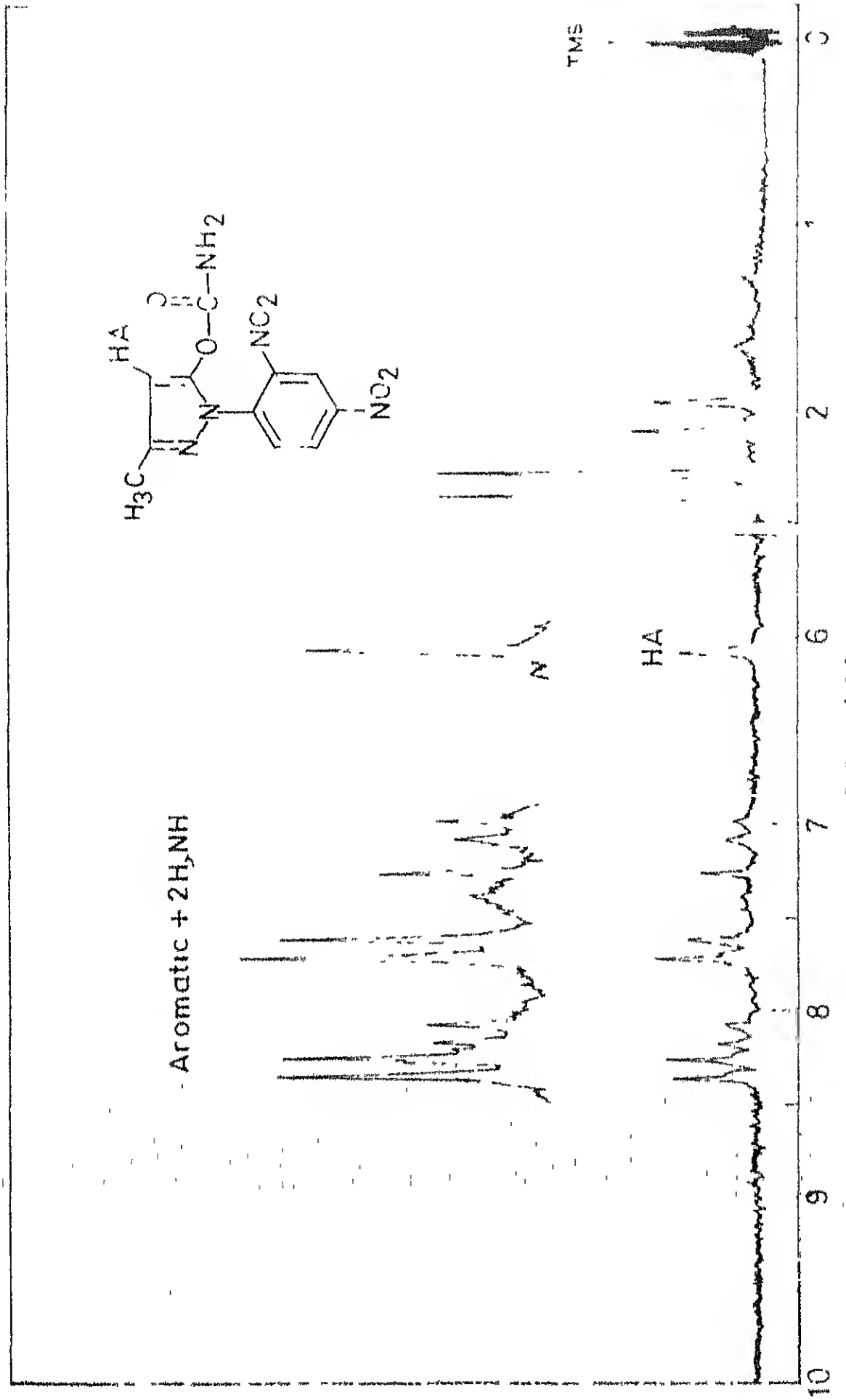


FIG. 1.10 PMR SPECTRUM (90 MHz) OF 194g

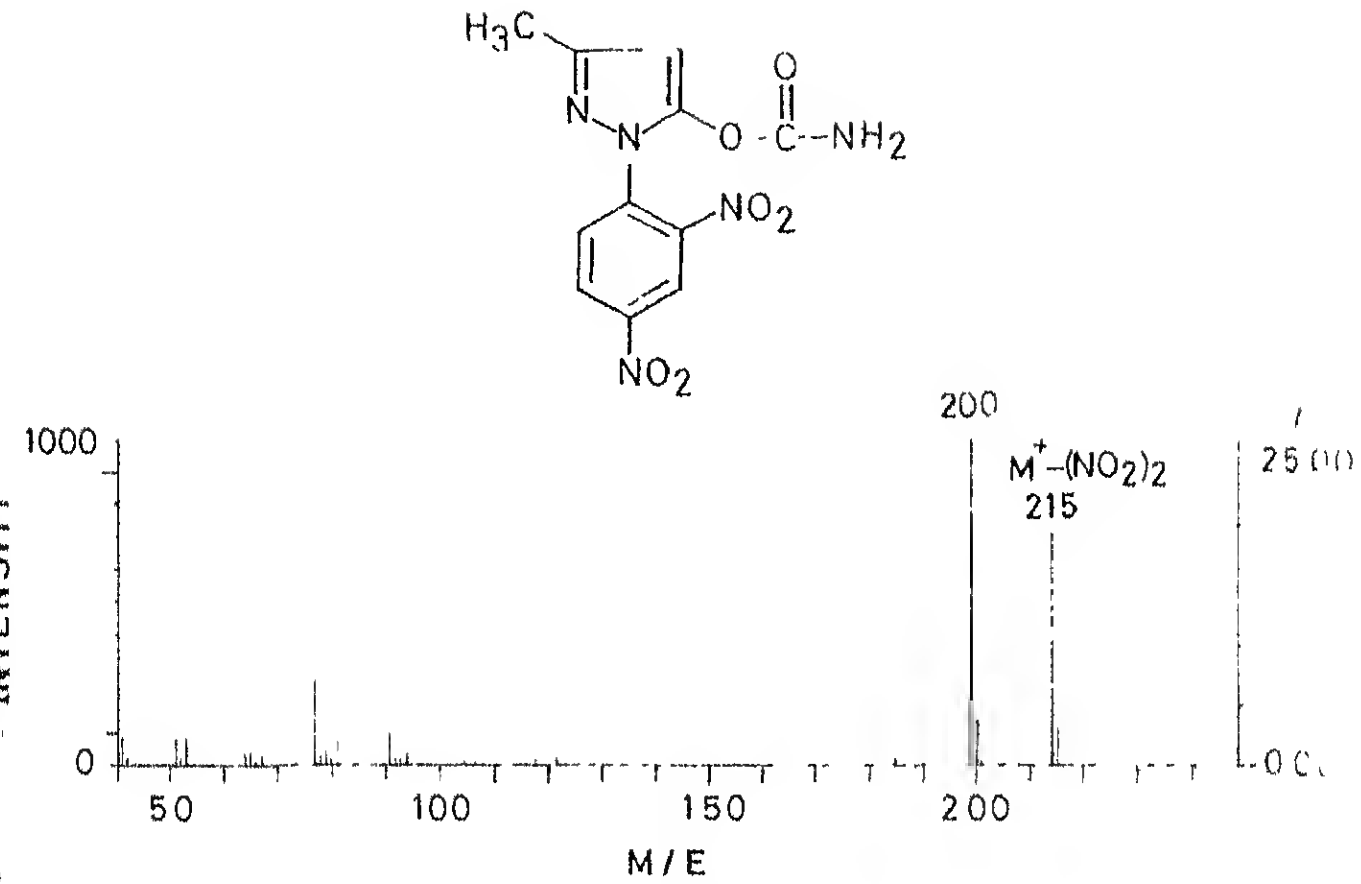


FIG. I.11 MASS SPECTRUM OF 194 g.

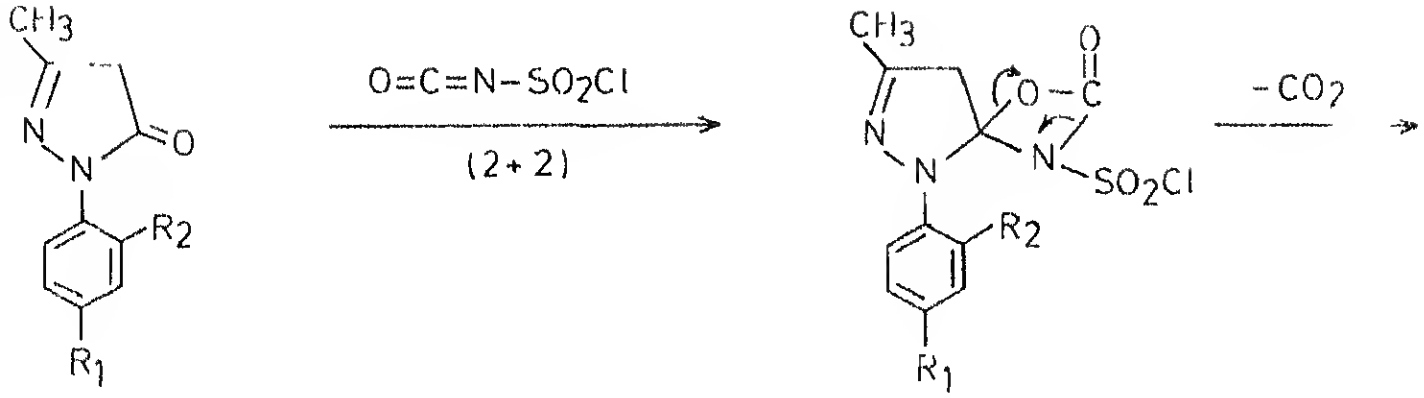
spectrum (Fig.I.13). It exhibited IR absorption bands at 3300 (ν_{NH}),1610($\nu_{C=N}$)cm^{-1},it revealed the disappearance of >C=O group of 2-pyrazolin-5-one (Fig.I.12). It exhibited PMR signals at δ 2.0 (s, 3H, CH_3), 2.2 (s, 2H, CH_2), 7.2-8.2 (m, 4H, aromatic), 11.0 (b, 1H, NH) exchangeable with D_2O. It was identified as 1-[4-Nitro phenyl]-3-methyl-2-pyrazolin-5-imide (198k).

On the basis of elemental analysis (1981) corresponded to molecular formula $C_{10}H_9N_5O_4$. It gave molecular ion peak at 263 in the mass spectrum. It displayed IR absorption bands at 3350 (ν_{NH}),1605($\nu_{C=N}$)cm^{-1},it gave PMR signals at δ 7.8-9.1 (m, 3H, aromatic), 2.1 (s, 3H, CH_3), 2.2 (s, 2H, CH_2), 11.0 (b, 1H, NH) exchangeable with D_2O (Fig.I.14). It was identified as 1-[2,4-dinitro phenyl]-3-methyl-2-pyrazolin-5-imide (1981).

Reaction of 3,5-dimethylisoxazole (199m) and 4-phenyl-3-methyl-5-amino-isoxazole (202n) with CSI took place smoothly producing 3,5-dimethyl-isoxazol-4-sulphonamide (201m) and 5-[3-methyl-4-phenyl]-isoxazolyl-urea (204n) respectively, as shown in Scheme I.60-61.

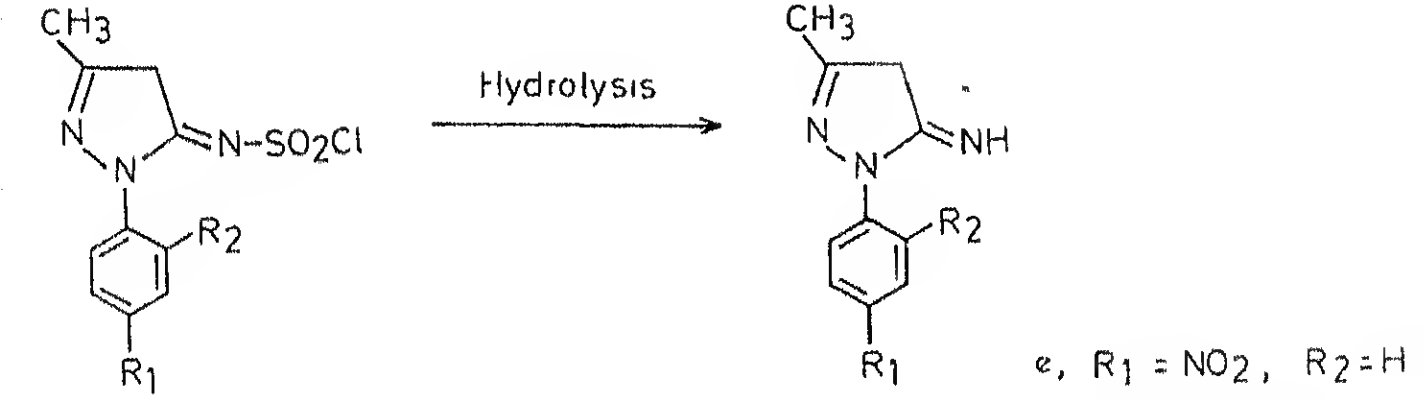
On the basis of elemental analysis (201m) corresponded to molecular formula $C_5H_8N_2O_3S$. Molecular ion peak appeared at 176 in the mass spectrum. It exhibited IR absorption bands located at 1595 ($\nu_{C=N}$), 3205, 3110 (ν_{NH_2}), 1160, 1345 (ν_{SO_2}) cm^{-1}, indicating the presence of (SO_2NH_2) group. It displayed PMR signals at δ 2.3(s, 3H, CH_3), 2.6 (s, 3H, CH_3), 6.2 (b, 2H, NH_2)

SCHEME 1.59



195 e · f

196



197

198

e, $R_1 = NO_2$, $R_2 = H$

f, $R_1 = R_2 = NO_2$

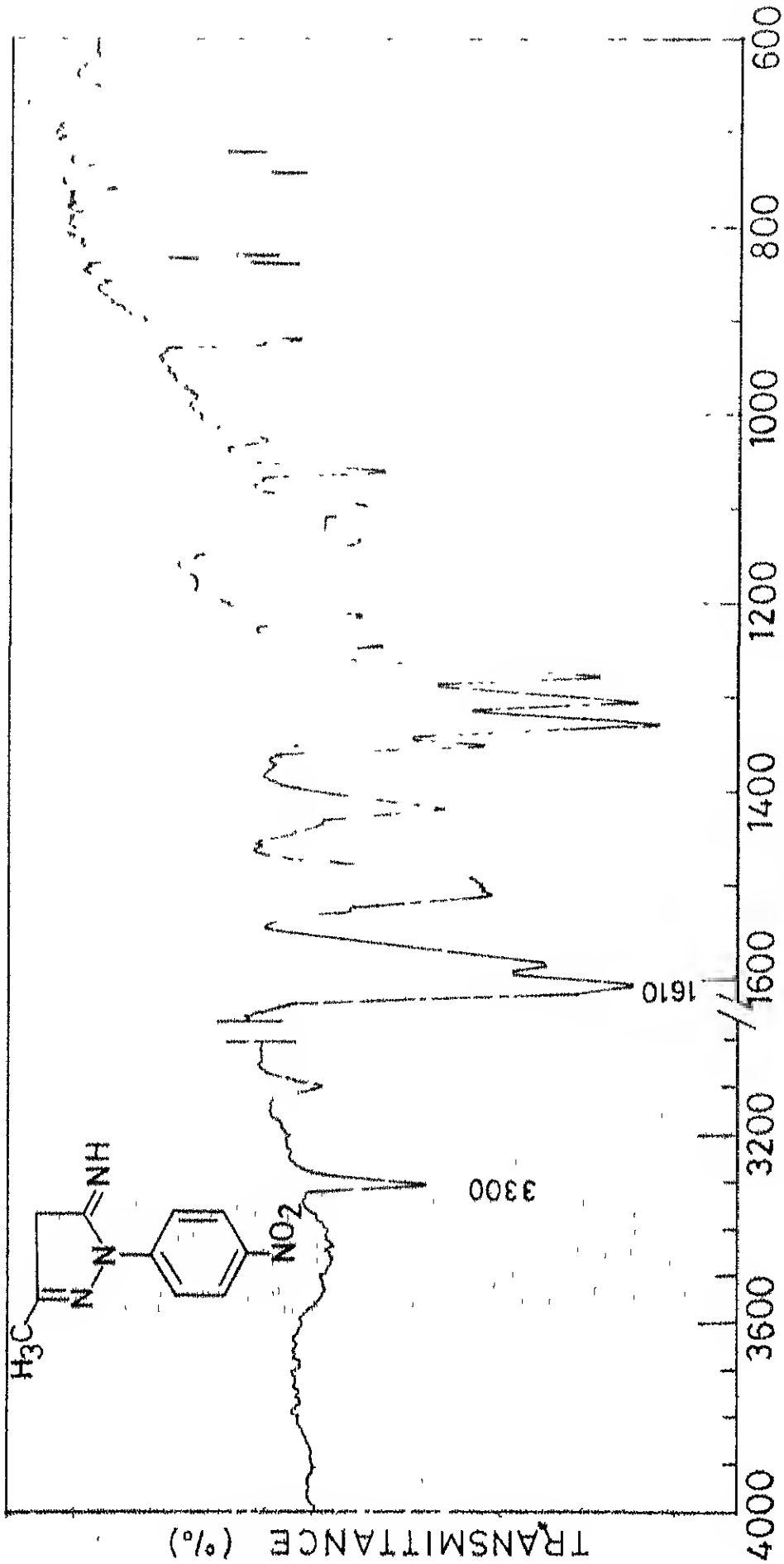


FIG. 12 IR SPECTRUM OF 198 k.

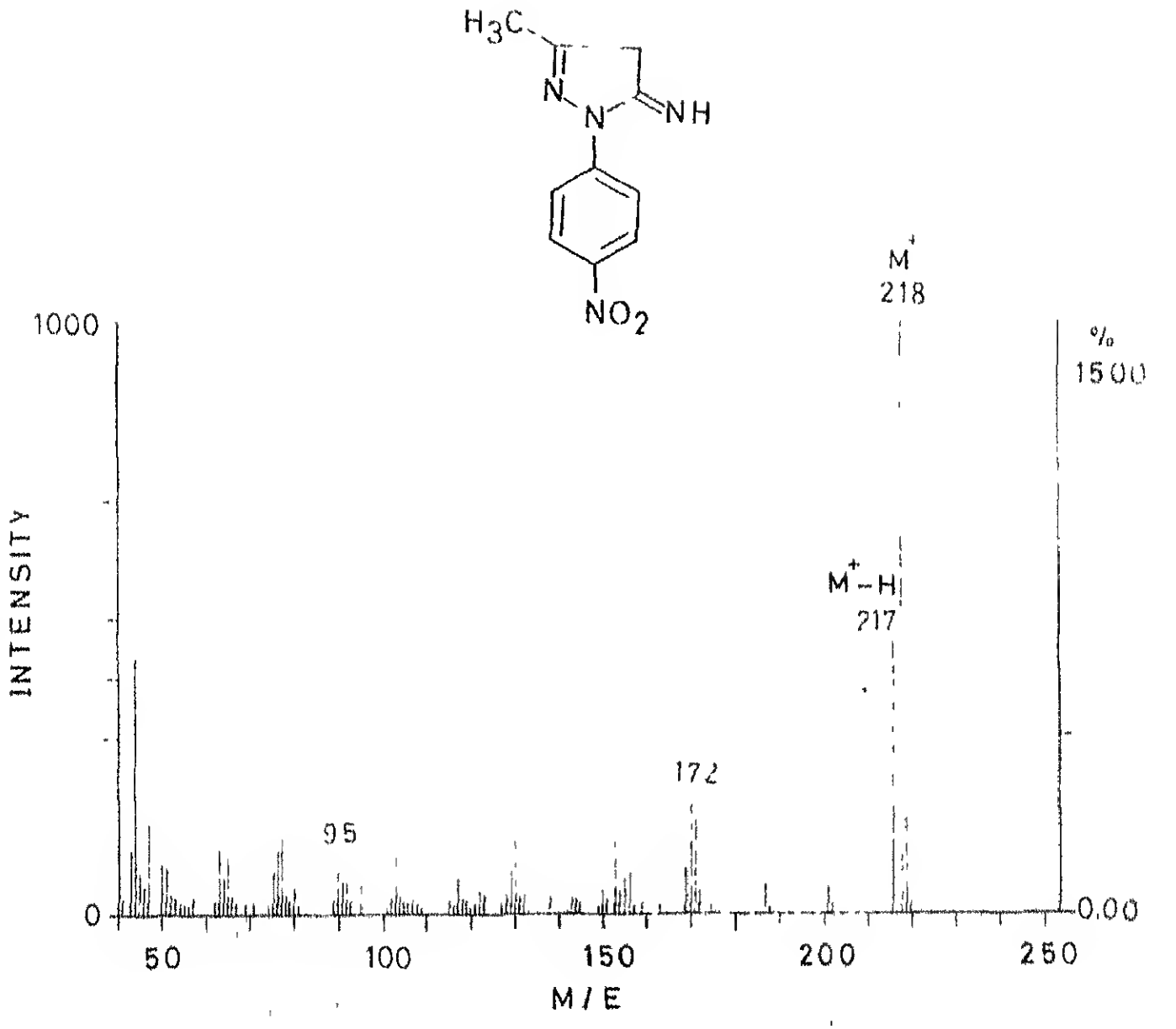


FIG. I.13 MASS SPECTRUM OF 198 k.

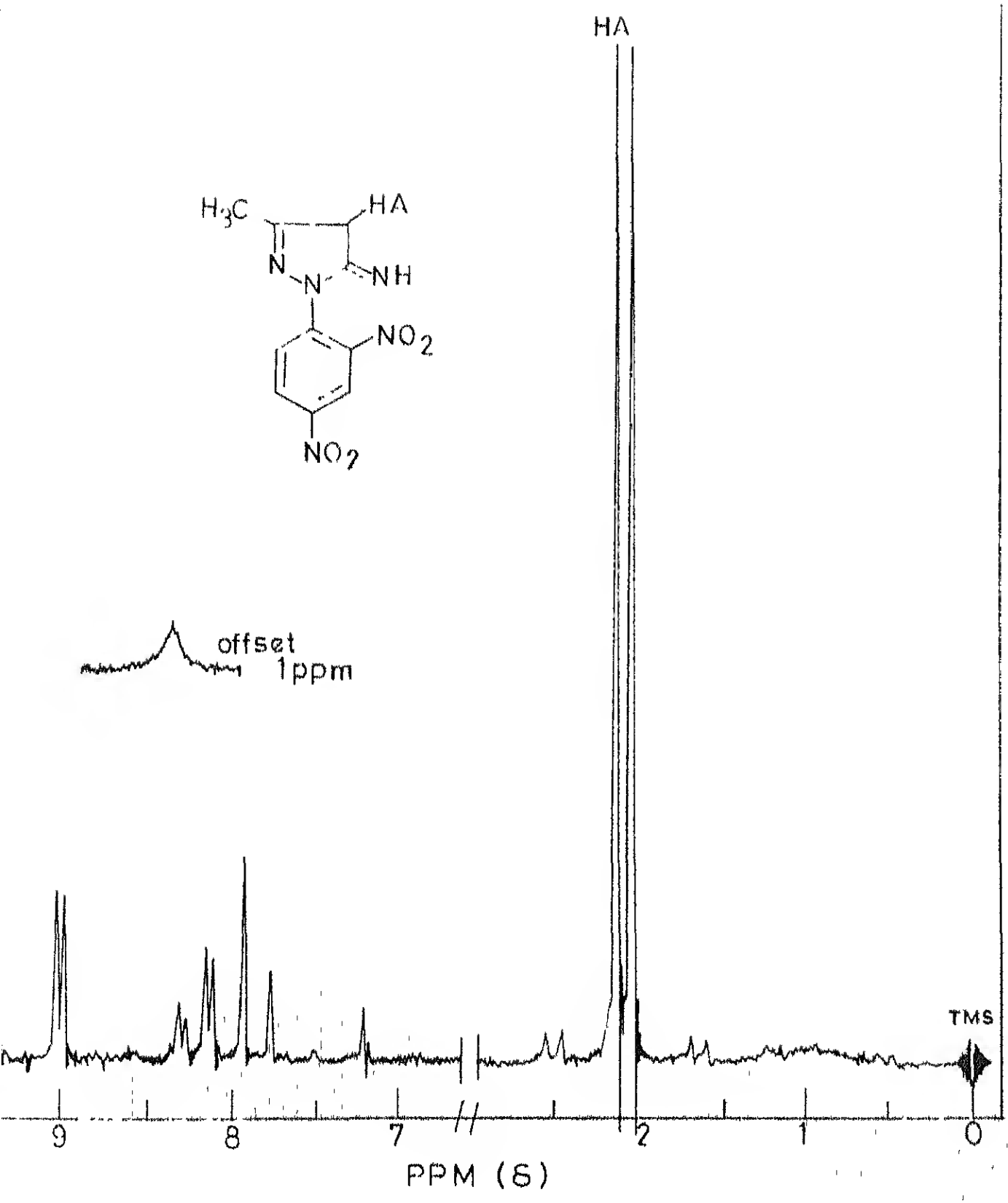


FIG. I.14 PMR SPECTRUM (90 MHz) OF 198L.

exchangeable with D_2O. It was identified as 3,5-dimethyl-isoxazol-4-sulphonamide (201m). On the basis of elemental analysis (204n) corresponded to the molecular formula $C_{11}H_{10}N_3O_2$. It gave molecular ion peak at 217 in the mass spectrum. It showed IR absorption bands at 3340,3440(ν_{NH_2}),1720($\nu_{C=O}$) cm^{-1}. It exhibited PMR signals at δ 2.2 (s, 3H, CH_3), 6.1 (b, 2H, NH_2) exchangeable with D_2O, 7.25(s, 5H, aromatic) (Fig.I.15). It was identified as 5-[3-methyl-4-phenyl]-isoxazoyl-urea (204n).

Reaction of 6-Nitro-1,2,3,4-tetrahydro-carbazole (205o), 6,8-dinitro-1,2,3,4-tetrahydrocarbazole (205p) with CSI at 0°, took place smoothly (Scheme I,62), producing 6-Nitro-1,2,3,4-tetrahydro-carbazol-N-chlorosulphonyl-carboximide (206o), 6,8-dinitro-1,2,3,4-tetrahydro-carbazol-N-chlorosulphonyl-carboximide (206p). The latter compound on hydrolysis, yielded 6,8-dinitro-1,2,3,4-tetrahydrocarbazol-N-carboximide (207p). On the basis of elemental analysis (206o) corresponded to molecular formula $C_{13}H_{12}ClN_2O_5S$. It gave molecular ion peak at 343 in the mass spectrum. It displayed IR absorption maxima at 1720 ($\nu_{C=O}$), 3260(ν_{NH}), 1340 (ν_{SO_2}) cm^{-1}, indicating the presence of chlorosulphonyl-carboximide group ($-\overset{O}{\overset{\|}{C}}-NHSO_2Cl$) (Fig.I.16). It showed PMR signals at δ 7.8-8.5 (m, 3H, aromatic), 6.0 (b, 1H, NH) exchangeable with D_2O, 2.2 (s, 8H, CH_2). It was identified as 6-Nitro-1,2,3,4-tetrahydro-carbazol-N-chlorosulphonyl-carboximide (206o).

On the basis of elemental analysis (207p) corresponded to molecular formula $C_{13}H_{12}N_4O_5$. It gave molecular ion peak at 304, in the mass spectrum. It gave IR absorption bands at 3190, 3340 (ν_{NH_2}), 1635($\nu_{C=O}$) cm^{-1}, showing the presence of amide group ($-\overset{O}{\overset{\|}{C}}-NH_2$). It exhibited PMR signals at δ 7.5-8.4 (m, 2H, aromatic), 5.0 (b, 2H, NH_2) exchangeable with D_2O, 2.3 (s, 8H, CH_2). It was identified as 6,8-dinitro-1,2,3,4-tetrahydrocarbazol-N-carboximide (207p).

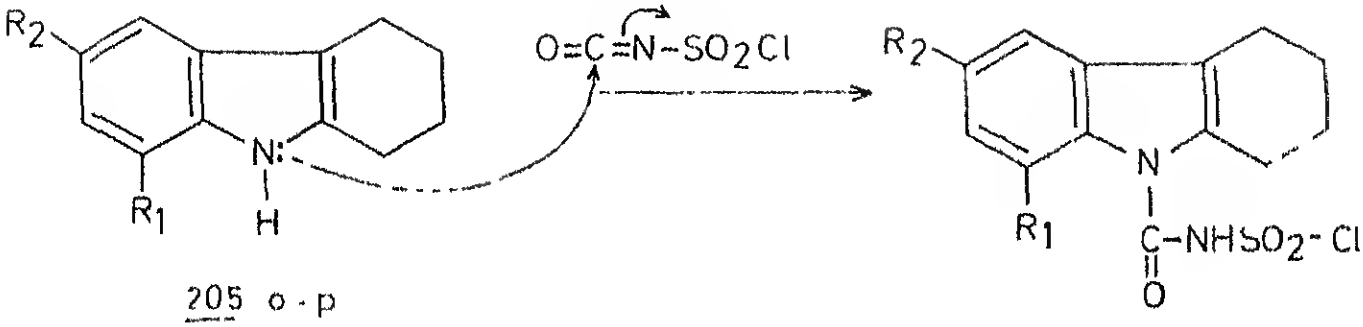
It is interesting to note that the attempted reaction of CSI with 1-[4-Nitro-phenyl]-3,5-dimethyl-pyrazole (184h), 1-[2,4-dinitro-phenyl]-3,5-dimetnyl-pyrazole (184i), 1-[2,4-dinitro-phenyl]-3-methyl-5-phenyl-pyrazole (184j) failed to yield any product. This observation can be rationalized as follows; the zwitterion formation in this case is not favoured, because of the absence of proton on nitrogen at position-2.

IR: ν_{max}(neat) cm^{-1}: 3200(ν_{NH}), 1700 ($\nu_{C=O}$), 1170, 1360(ν_{SO_2}).

I.4 EXPERIMENTAL

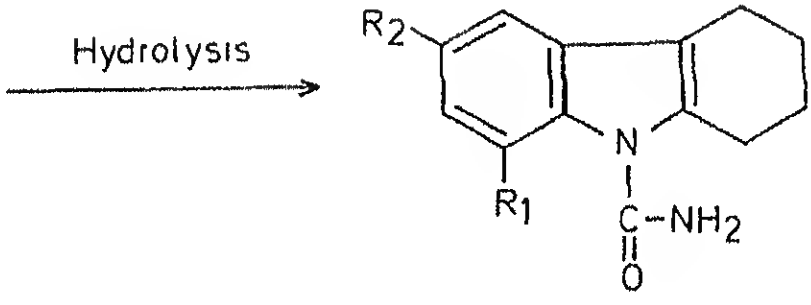
All the melting points are uncorrected and were taken on a Fisher-Johns melting-point apparatus. The IR spectra were recorded on Perkin-Elmer model-580 infrared spectrophotometers. Proton magnetic resonance (PMR) spectra were recorded on Varian EM-390(90 MHz) instrument. Chemical shifts are reported in parts per million down field from the internal reference TMS(δ). Multiplicity is indicated using the following abbreviations:

SCHEME I.62



205 o - p

206



207

o , $R_1 = H$, $R_2 = NO_2$

p , $R_1 = R_2 = NO_2$

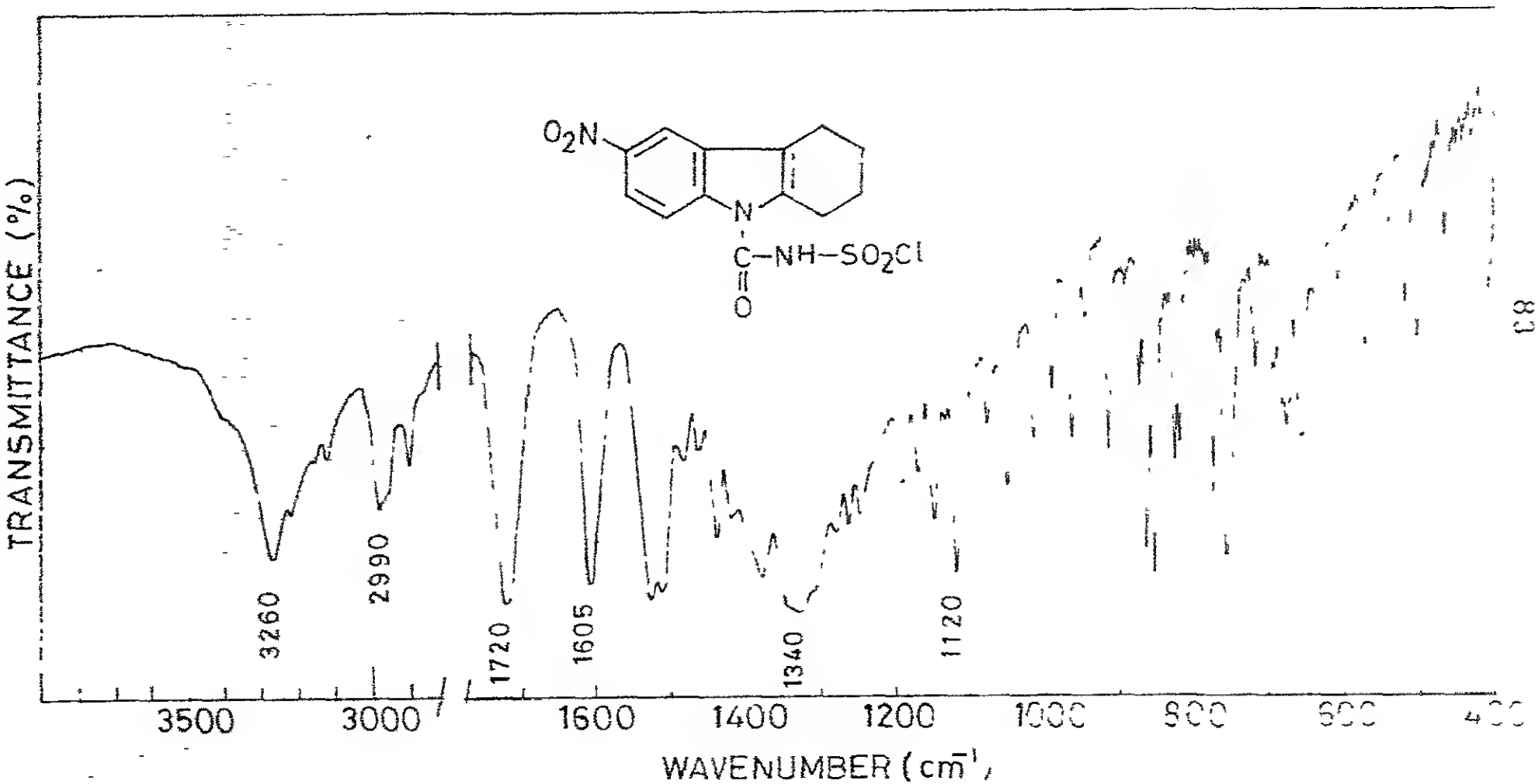


FIG. 1.16 IR SPECTRUM OF 206 o.

S(singlet), bs(broad singlet), d(doublet), t(triplet), q(quartet) and m(multiplet). Mass spectra were recorded on a Jeol JMS-300D mass spectrometer at 70 eV. The elemental analyses were carried out in coleman automatic carbon, hydrogen and nitrogen analysers.

Starting materials

Chlorosulphonyl isocyanate was purchased from Fluka AG, Switzerland and was used as such. The pyrazoles, 2-pyrazolin-5-ones, 1,2,3,4-tetrahydrocarbazoles and isoxazoles were prepared in accordance with the procedure described in the literature. Pyrazoles[122-123] were prepared by the action of hydrazine or substituted hydrazines on 1,3-diketones. The reaction proceeds via ring closure of the initially formed hydrazone. 2-pyrazolin-5-ones[124-125] were prepared by the condensation of ethylaceto-acetate, ethyl benzoyl acetate and their derivatives with various phenyl-hydrazones. The initially formed phenyl-hydrazones were cyclized to give the corresponding 2-pyrazolin-5-ones. The isoxazoles[126] were prepared by treating 1,3-diketones with hydroxyl-amine-hydrochloride. The product of the reaction was a monoxime which on subsequents cyclization yielded the corresponding isoxazole. 1,2,3,4-tetrahydrocarbazoles[127-128] were prepared by reaction of cyclo-hexanone and its derivatives with various phenyl hydrazines. Phenyl-hydrazonesof cyclohexanone were cyclized in presence of glacial acetic acid to furnish 1,2,3,4-tetrahydro-carbazoles.

Synthesis of 3,5-Dimethylpyrazol-1-N-chlorosulphonyl-carboximide

To a stirred solution of 3,5-dimethyl pyrazole (0.01 mol) in dry dichloromethane (10 ml) was added dropwise chlorosulphonyl isocyanate (0.01 mol) in dichloromethane (2 ml) during 10 min at 0° (ice-bath). The stirring was continued for 15 min., solvent was removed under reduced pressure. Residue obtained was recrystallized from toluene/pet ether, yielding 3,5-dimethyl-pyrazol-1-N-chlorosulphonyl-carboximide (185a) yield: 1.73g, (73%), m.p.159-60°.

Anal for $C_6H_8ClN_3O_3S$: Calcd; C, 30.37; H, 3.37; N, 17.72%
Found; C, 31.05; H, 4.12; N, 18.10%

IR Spectrum(KBr), ν_{max}: 3115(ν_{NH}), 1695($\nu_{C=O}$), 1150, 1345(ν_{SO_2}) cm^{-1}.

PMR Spectrum($DMSOd_6$), δ ppm: 2.13(s, 6H, CH_3), 5.7 (s, 1H, CH), 14.0(b, 1H, NH), exchangeable with D_2O.

Mass spectrum, m/e: 237(M^+), 207, 138.

3,5-Dimethyl-pyrazol-1-N-sulphonamide (188a)

To a stirred solution of 3,5-dimethyl-pyrazole (0.01 mol) in dry dichloromethane (10 ml), chlorosulphonyl-isocyanate (0.01 mol) in dichloromethane (2 ml) was added dropwise during 10 min at 0°. The stirring was continued for 15 min and then solvent was removed in vacuo. The residue thus obtained was dissolved in acetone-water (4:1, 10 ml) and neutralized by the addition of 10% aqueous KOH. After stirring it for 0.5 hr it was diluted with

water (15 ml) and extracted with ethyl acetate (3x2 ml). The combined organic extracts were dried (Na_2SO_4) and solvent removed under diminished pressure. Recrystallization from aqueous ethanol furnished 3,5-dimethyl-pyrazol-N-sulphonamide (188a). Yield:1.225g, (70%), 115-116°.

Anal for $C_5H_9N_3O_2S$: Calcd; C, 34.28; H, 5.14; N, 24.0%
Found; C, 35.00; H, 4.88; N, 25.12%

IR Spectrum(KBr) ν_{max}: 3200, 3110(ν_{NH_2}), 1160, 1310(ν_{SO_2}) cm^{-1}.

PMR Spectrum($DMSOd_6$), δ ppm: 2.2(s, 6H, CH_3CH_3, 5.92 (s, 1H, CH), 15(b, 2H, NH_2), exchangeable with D_2O.

Mass spectrum, m/e: 95($M^+-SO_2NH_2$).

Pyrazol-1-N-sulphonamide(188c)

The preparation of the titled compound is similar to that described for the preparation of 3,5-dimethyl-pyrazol-1-N-sulphonamide (188c). It was recrystallized from aqueous ethanol. Yield: 0.882g, (60%), m.p. 127-128°.

Anal for $C_3H_5N_3O_2S$: Calcd; C, 24.48; H, 3.40; N, 28.57%
Found; C, 23.60; H, 4.26; N, 29.12%

IR Spectrum(KBr), ν_{max}: 3210, 3120 (ν_{NH_2}), 1165,1330(ν_{SO_2}) cm^{-1}.

PMR Spectrum ($DMSOd_6$), δ ppm: 14(b, 2H, NH_2), Ha: (d, J=7Hz), Hb:(t, J=7Hz), Hc:(d, J=7Hz).

Mass spectrum, m/e: 147(M^+), 67($M^+-SO_2NH_2$).

3-Methyl-5-ethoxy-pyrazol-1-N-chlorosulphonyl-carboximide (185b)

The preparation of the above compound is similar to that described for the preparation of 3,5-dimethyl-pyrazol-1-N-chlorosulphonyl-carboximide (185a). It was recrystallized from toluene/pet ether, Yield: 1.63g, (61%), m.p. 125-126°.

Anal for $C_7H_{10}ClN_3O_4S$: Calcd, C, 31.46; H, 3.74; N, 15.73%
Found, C, 30.79; H, 4.12; N, 16.01%

IR Spectrum(KBr), ν_{max}: 3290(ν_{NH}), 1700($\nu_{C=O}$), 1150, 1340(ν_{SO_2}) cm^{-1}.

PMR Spectrum($MDSOd_6$), δ ppm: 1.1-1.2(q, 3H, CH_3), 2.1(s, 3H), 4.1 (q, 2H, C_2H_5), 14(b, 1H, NH), exchangeable with D_2O.

Mass spectrum, m/e: 169(M^+-SO_2Cl), 125($M^+-CONHSO_2Cl$).

3-Methyl-5-ethoxy-pyrazol-1-N-carboximide (186d)

The above named compound was prepared in an analogous manner to that described under the preparation of 3,5-dimethyl-pyrazol-1-N-sulphonamide. The desired compound in the pure form was isolated by recrystallization from ethanol. Yield: 1.83g, (70%), m.p. 115-116°.

Anal for $C_7H_{11}N_3O_2$: Calcd, C, 49.70; H, 6.50; N, 24.85%
Found, C, 48.86; H, 7.52; N, 25.12%

IR Spectrum (KBr): ν 3280, 3340 (ν_{NH_2}), 1660 ($\nu_{C=O}$), 1600 ($\nu_{C=N}$) cm^{-1}.

PMR spectrum (DMSOd_6) δ ppm: 2.3 (s, 3H, CH_3), 1.1-1.3 (q, 3H, CH_3), 4.0 (q, 2H, C_2H_5), 6.08 (s, 1H, CH), 13.0 (b, 2H, NH_2), exchangeable with D_2O.

Mass spectrum, m/e: 169 (M^+).

1-[4-Nitro-phenyl]-3-methyl-5-ethoxy-pyrazol-4-chlorosulphonyl-carboximide (190)

The preparation of the titled compound is similar to that described for the preparation of 3,5-dimethyl-pyrazol-1-N-chloro-sulphonyl-carboximide. It was purified by recrystallization from toluene/pet ether, Yield : 2.33g, (60%), m.p. 117-178°.

Anal for $C_{13}H_{13}ClN_4O_6S$: Calcd, C, 40.20; H, 3.35; N, 14.43 %
Found, C, 40.15; H, 3.29; N, 14.44%

IR Spectrum (KBR) ν_{max}: 3210 (ν_{NH}), 1700 ($\nu_{C=O}$), 1170, 1350 (ν_{SO_2}) cm^{-1}.

PMR Spectrum (Acetone d_6) δ ppm: 1.2 (t, 3H, CH_3), 2.2 (s, 3H), 4.1 (d, 2H) C_2H_5, 8.% (s, 4H, aromatic), 6.2 (b, 1H, NH).

Mass spectrum, m/e: 388 (M^+), 289 (M^+-SO_2Cl), 246, 200.

1-[4-Nitro-phenyl]-3-methyl-5-ethoxy-pyrazol-4-carboximide (191d)

The preparation of the above compound is similar to that described for the preparation of 3,5-dimethyl-1-N-sulphonamide.

It was purified by recrystallization from ethanol. Yield :2.03g, (70%), m.p.203-205°.

Anal for $C_{13}H_{14}N_4O_4$: Calcd, C, 53.79; H, 4.82, N, 19.31%
Found, C, 53.78; H, 4.83; N, 19.30%

IR Spectrum(KBr) ν_{max} : 3205, 3380 (ν_{NH_2}), 1680 ($\nu_{C=O}$).cm^{-1}.

PMR Spectrum (Aceton d_6) δ ppm: 1.2 (t, 3H, CH_3), 2.2 (s, 3H),
4.1 (d, 2H)C_2H_5, 8.5 (s, 4H, aromatic),
6.2 (b, 2H, NH_2), exchangeable with D_2O.

Mass spectrum, m/e: 290(M^+), 246, 244, 123.

1-[4-Nitro-phenyl]-3-methyl-5-ethoxy-pyrazol-4-carbonitrile(192d)

To a stirred solution of 1-[4-Nitro-phenyl]-3-methyl-5-ethoxy-pyrazole (0.025 mol) in dry dichloromethane (8 ml) was added CSI(0.025 mol) in CH_2Cl_2 (2 ml) over a period of 5 min at 0°. Reaction mixture was stirred for 30 min. Dry DMF (0.05 mol) in dichloromethane (5 ml) was added dropwise. The stirring was continued for 2 hr and the reaction mixture was poured into ice-cold water (10 ml), and extracted with CH_2Cl_2 (10 ml x 3). All the organic extracts were mixed and dried (Na_2SO_4) and the solvent stripped off under diminished pressure. The residue on recrystallization, from aqueous ethanol, furnished 1-[4-Nitro-phenyl]-3-methyl-5-ethoxy-pyrazol-4- carbonitrile. Yield :1.768g, (65%), m.p.169-170°.

Anal for $C_{13}H_{12}N_4O_3$: Calcd, C, 57.35; H, 4.41; N, 20.58%
Found, C. 56.94; H, 5.10; N, 21.12%

IR Spectrum(KBr), ν_{max}: 2135, 2330($\nu_{C=N}$), 1565($\nu_{C=N}$) cm^{-1}.

PMR Spectrum (Aceton d_6), δ ppm: 1.1-1.3(q, 3H, CH_3), 2.20(s, 3H), 4.12(q, 2H, C_2H_5), 7.8-8.3(m, 4H, aromatic).

Mass spectrum, m/e: 272(M^+), 246(M^+-CN), 123.

1-Phenyl-3-methyl-5-carbamato-pyrazole (194e)

The titled compound was prepared as described for the preparation of 1-[4-nitrophenyl]-3-methyl-2-pyrazolin-5-imide. It was purified by recrystallization from ethanol. Yield: 1.32g, (60%), m.p. 189-190°.

Anal for $C_{11}H_{11}N_3O_2$: Calcd, C, 60.82; H, 5.06; N, 19.35%
Found, C, 59.67; H, 4.76; N, 20.12%

IR Spectrum (KBr), ν_{max}: 1770($\nu_{C=O}$), 3120, 3360(ν_{NH_2}) cm^{-1}.

PMR Spectrum($CDCl_3$), δ ppm: 7.4-8.4(m, 5H, aromatic + 2H, NH), 6.0(s, 1H, CH), 1.9-2.8(q, 3H, CH_3).

Mass spectrum, m/e: 217(M^+), 140(M^+-C_6H_5), 140.

1-[4-Nitrophenyl]-3-methyl-5-carbamato-pyrazole (194f)

The titled compound was prepared as described under the preparation of 1-[4-nitrophenyl]-3-methyl-2-pyrazolin-5-imide. It was purified by recrystallization from ethanol. Yield: 1.57g, (60%), m.p. 151-152°.

Anal for $C_{11}H_{10}N_4O_4$: Calcd, C, 50.38; H, 3.81; N, 21.37%
Found, C, 50.95; H, 4.61; N, 20.10%

IR Spectrum(KBr), ν_{max}: 1770($\nu_{C=O}$), 3120, 3360(ν_{NH_2}) cm^{-1}.

PMR Spectrum($CDCl_3$), δ ppm: 7.1-8.4(m, 4H, aromatic + 2H, NH), 6.1(s, 1H, CH), 1.9-2.5(q, 3H, CH_3).

Mass spectrum, m/e: 262(M^+), 216(M^+-NO_2), 201.

1-[2,4-Dinitrophenyl]-3-methyl-5-carbamato-pyrazole (194g)

The aforementioned compound was prepared as described under the preparation of 3,5-dimethyl-pyrazol-1-N-sulphonamide. It was purified by recrystallization from ethanol. Yield: 1.87g, (61%), oil.

Anal for $C_{11}H_9N_5O_6$: Calcd, C, 42.99; H, 2.93; N, 22.80%
Found, C, 41.39; H, 3.32; N, 21.51%

IR Spectrum($CHCl_3$), ν_{max}: 1750($\nu_{C=O}$), 3140, 3360(ν_{NH_2}) cm^{-1}.

PMR Spectrum($CDCl_3$), δ ppm: 7.2-8.4(m, 3H, aromatic + 2H, NH), 6.1(s, 1H, CH), 1.9-2.5(q, 3H, CH_3).

Mass spectrum, m/e: 215(M^+-$(NO_2)_2$, 200.

1-[4-Nitro phenyl]-3-methyl-5-imino-2-pyrazolin(198k)

To a stirred solution of 1-[4-Nitro-phenyl]-3-methyl-2-pyrazolin-5-one (0.01 mol) in dry dichloromethane (10 ml) maintained at 0°C, CSI (0.01 mol) in dichloromethane (2 ml) was added dropwise over a period of 5 minutes. The reaction mixture was stirred for 15 min, followed by pouring it on to cold-water (10 ml) and extracted with ethyl acetate (3 x 2 ml). The combined organic extracts were dried (Na_2SO_4) and solvent removed under reduced pressure. The residue on recrystallization from aqueous-ethanol furnished 1-[4-Nitro-phenyl]-3-methyl-5-imino-2-pyrazoline.

Yield:1.39g,(62%), m.p. 95-96° (lit. m.p. 97°).

Anal for $C_{10}H_{10}N_4O_2$: Calcd, C, 55.04; H, 4.58; N, 25.68 %

Found, C, 55.00; H, 4.59; N, 25.65%

IR Spectrum (KBr) ν_{max} : 3300, 3090 (ν_{NH}), 1610($\nu_{C=N}$),1500,740,720 cm^{-1}.

PMR Spectrum (Acetone-d_6) δ 2.0(s, 3H, CH_3), 2.2 (s, 2H, CH_2), 7.2-8.2 (m, 4H, aromatic), 11.0 (b, 1H, NH) exchangeable with D_2O.

Mass spectrum, m/e: 218(M^+), 217, 172, 95.

1-[2,4-Dinitrophenyl]-3-methyl-5-imino-2-pyrazoline (198l)

The preparation of the titled compound is analogous to the preparation of (198k). It was purified by recrystallization from aqueous ethanol. Yield: 2.23g, (85%), 128-129°.

Anal for $C_{10}H_9N_5O_4$: Calcd, C, 45.62; H, 3.42; N, 26.61%
Found, C, 46.10; H, 2.75; N, 25.84%

IR Spectrum(KBr), ν_{max}: 3310(ν_{NH}), 1605($\nu_{C=N}$) cm^{-1}.

PMR Spectrum($CDCl_3$), δ ppm: 7.8-9.1(m, 3H, aromatic), 2.1 (s, 3H, CH_3), 2.2 (s, 2H, CH_2).

Mass spectrum, m/e: 263(M^+), 262, 171, 94.

3,5-Dimethyl-isoxazol-4-sulphonamide(201m)

The above named compound was prepared in a similar way as that described under the preparation of 3,5-dimethyl-pyrazol-1-N-sulphonamide. It was purified by recrystallization from ethanol. Yield: 1.23g, (70%), m.p. 157-158°.

Anal for $C_5H_8N_2O_3S$: Calcd, C, 34.09; H, 4.54; N, 15.90%
Found, C, 35.46; H, 5.61; N, 16.10%

IR Spectrum(KBr), ν_{max}: 1595($\nu_{C=N}$), 3205, 3110(ν_{NH_2}), 1160, 1345 (ν_{SO_2}) cm^{-1}.

PMR Spectrum($DMSOd_6$), δ ppm: 2.3(s, 3H, CH_3), 2.0(s, 3H, CH_3), 6.2(b, 2H, NH_2), exchangeable with D_2O.

Mass spectrum, m/e. 176(M^+), 96.

5-[3-Methyl-4-phenyl]-isoxazolyl-urea (204n)

The titled compound was prepared in an similar fashion to that described for the preparation of (198k). It was purified by recrystallization from aqueous ethanol. Yield: 1.63g, (75%), m.p. 196-197°.

Anal for $C_{11}H_{11}N_3O_2$: Calcd, C, 60.83; H, 5.07; N, 19.35%
Found, C, 59.90; H, 6.43; N, 20.10%

IR Spectrum(KBr), ν_{max}: 3340, 3440(ν_{NH_2}), 1720($\nu_{C=O}$) cm^{-1}.

PMR Spectrum($DMSOd_6$), δ ppm: 2.1(s, 3H, CH_3), 6.1 (b, 2H, NH_2), exchangeable with D_2O, 7.25 (s, 5H, aromatic).

Mass spectrum, m/e: 217(M^+), 158.

6-Nitro-1,2,3,4-tetrahydro-carbazol-N-chlorosulphonyl-carboximide (206o)

The preparation of the titled compound is similar to that described under the preparation of 1-[4-nitrophenyl]-3-methyl-2-pyrazolin-5-imide. It was purified by recrystallization from ethanol. Yield: 2.40g, (70%), m.p. 177-178°.

Anal for $C_{13}H_{12}ClN_2O_5S$: Calcd, C, 45.48; H, 3.49; N, 8.16%
Found, C, 46.01; H, 2.98; N, 9.12%

IR Spectrum (KBr) ν_{max} : 3260 (ν_{NH}), 1720($\nu_{C=O}$), 1120, 1340 (ν_{SO_2}), 850, 750, 650 cm^{-1}.

PMR spectrum ($DMSOd_6$) δ ppm: 7.8-8.5 (m, 3H, aromatic), 6.0 (b, 1H, NH), 2.2 (s, 8H, CH_2).

Mass spectrum, m/e: 343(M^+), 244(M^+-SO_2Cl), 201.

6,8-Dinitro-1,2,3,4-tetrahydrocarbazol-N-carboximide(207p)

The preparation of the above compound was carried out in a manner described for the preparation of 1-[4-Nitro-phenyl]-3-methyl-2-pyrazolin-5-imide. It was purified by recrystallization from ethanol. Yield: 2.16g,(71%), m.p. 144-145°.

Anal for $C_{13}H_{12}N_4O_5$: Calcd, C, 51.31; H, 3.95; N, 18.42%
Found, C, 51.30; H, 3.65; N, 18.41%

IR Spectrum (KBr) ν_{max} : 3190, 3340 (ν_{NH_2}), 1635 ($\nu_{C=O}$), 750 cm^{-1}.

PMR Spectrum ($DMSOd_6$) δ ppm: 7.5-8.4 (m, 2H, aromatic), 5.0 (b, 2H, NH_2), exchangeable with D_2O, 2.3 (s, 8H, CH_2).

Mass spectrum, m/e: 304(M^+), 260($M^+-\overset{O}{\overset{\|}{C}}-NH_2$).

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CHAPTER-II

REACTION OF SULPHURYL CHLORIDE WITH SCHIFF'S BASES

ABSTRACT

The second chapter deals with the modified Ritter reaction of sulphuryl chloride with various schiff's bases in acetonitrile, benzonitrile, dimethyl sulphoxide and ethyl cyanoacetate respectively. N-substituted amides are preparable by Ritter's reaction which consists in the interaction of an olefin with acetonitrile in presence of sulphuric acid. Since its discovery in 1948, the Ritter reaction has been extended to a wide variety of compounds, capable of generating carbonium ions, and thus it has emerged as a very important synthetic reaction.[2-4] Chloroamination of olefins can be achieved by a "modified Ritter reaction" using sulphuryl chloride and acetonitrile (or benzonitrile). This prompted us to investigate the reaction of this reagent with various Schiff's bases.

The reaction of the following Schiff's bases with sulphuryl chloride (1:1, in acetonitrile) have been studied. N-[p-Bromo-benzylidene]-aniline, N-[p-chloro-benzylidene]-p-chloro aniline, N-[p-chloro benzylidene]aniline, N-[benzylidene]-p-chloro-aniline, N-[benzylidene]aniline, N-[benzylidene]-p-nitro-aniline, N-[p-nitro-benzylidene]-p-nitro-aniline, N-[p-nitro-benzylidene]-m-nitro-aniline, N-[p-nitro-benzylidene]-o-nitro-aniline, N-[benzylidene]-m-nitro-aniline, N-[benzylidene]-o-nitro-aniline, N-[p-bromo-benzylidene]-p-nitroaniline, N-[3,4-dimethoxybenzylidene]-m-nitro-aniline, N-[3,4-dimethoxy-benzylidene]-aniline, N-[3,4-dimethoxy-benzylidene]-p-chloro-aniline, N-[p-methoxy-benzylidene]-aniline, N-[p-methoxy-benzylidene]-p-chloro-aniline, N-[3,4-dimethoxy-benzylidene]-p-methoxy-aniline, and aldazines (97a-f).

The above modified Ritter reaction was studied with the following schiff's bases, in the presence of SO_2Cl_2-DMSO: N-[3,4-dimethoxy-benzylidene]-aniline, N-[3,4-dimethoxy-benzoylidene]-p-chloro aniline, N-[p-methoxy-benzylidene]-aniline, N-[p-methoxy-benzylidene]-p-chloro-aniline, N-[3,4-dimethoxy-benzylidene]-p-methoxy-aniline.

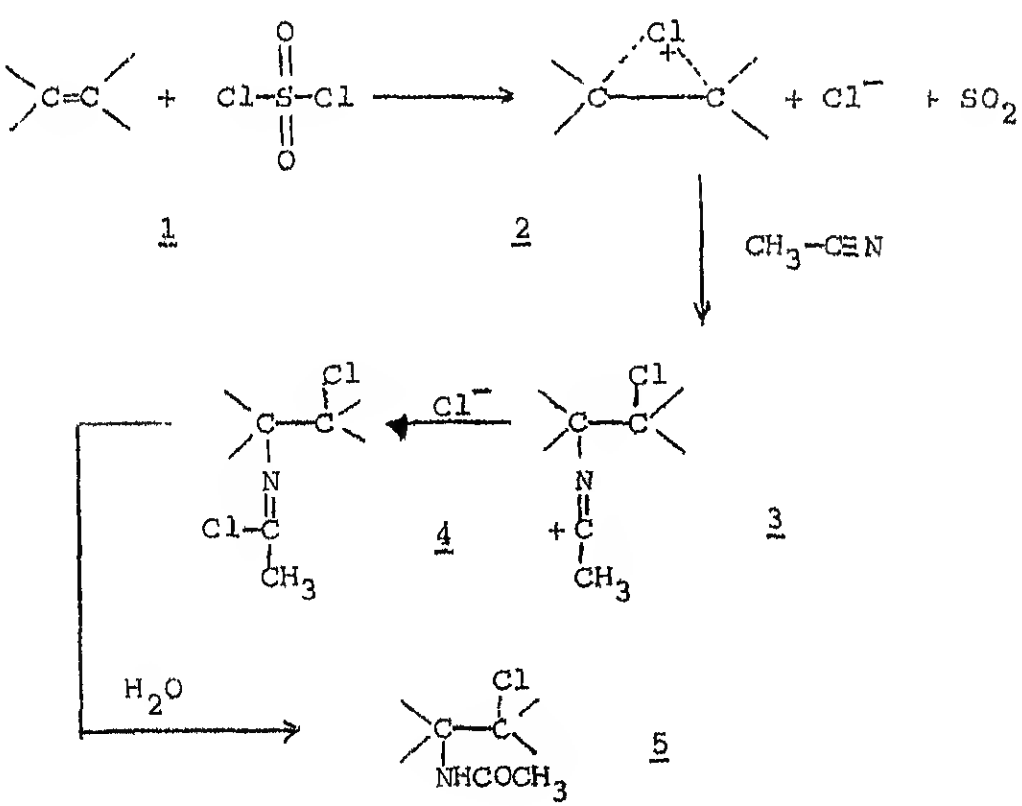
An analogous study has been made, involving the reaction of sulphuryl chloride-ethyl cyanoacetate with some of the Schiff's bases (*vide infra*), N-[benzylidene]-p-chloro-aniline, N-[benzylidene]-p-nitro-aniline, N-[benzylidene]-m-nitro-aniline, N-[p-nitro-benzylidene]-m-nitro-aniline.

Likewise the interaction of SO_2Cl_2-C_6H_5CN with the following Schiff's bases have been investigated: N-[benzylidene]-aniline, N-[p-chloro benzylidene]-p-chloro aniline, N-[benzylidene]-p-chloro aniline.

Dhar and Keshavamurthy[7] have exploited the modified Ritter reaction (SO_2Cl_2-CH_3CN/C_6H_5CN) in the synthesis of N-[2-chloroalkyl]-acetamides in good yields (60-72%). The olefins used in this reaction include cyclohexene, 1-octene, 1-undecene, trans-stilbene and styrene.

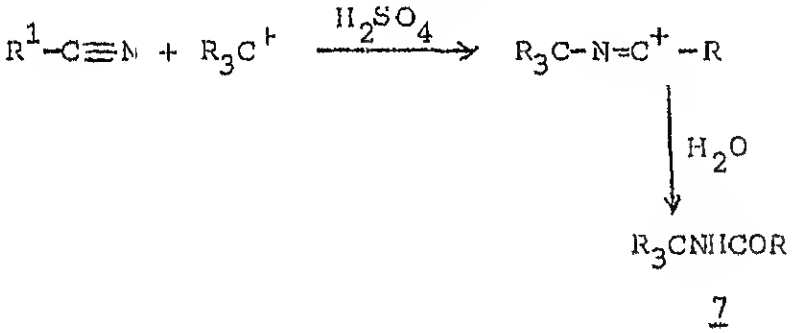
The plausible mechanism of the reaction is depicted in Scheme II.1.

Scheme II.1



In synthetic organic chemistry, alkene amination occupies an important position[1]. A general method of achieving this transformation is due to Ritter, named after him as Ritter[6] reaction. In the most general form the Ritter reaction involves the nucleophilic addition of nitrile to a carbonium ion generated in the presence of sulphuric acid. Subsequent dilution with water yields the amide (Scheme II.2). When HCN is employed as the nitrile component, the resulting N-alkylformamide can be readily hydrolysed to the corresponding carbinamine.[6] The mechanism suggested by Ritter and his coworkers[6] is illustrated in Scheme II.3 and is amply supported by the experimental facts.

Scheme II.2



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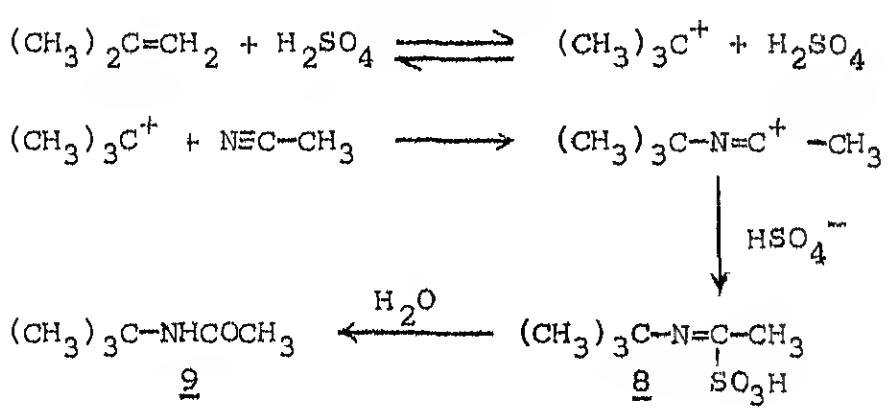
Scheme II.3



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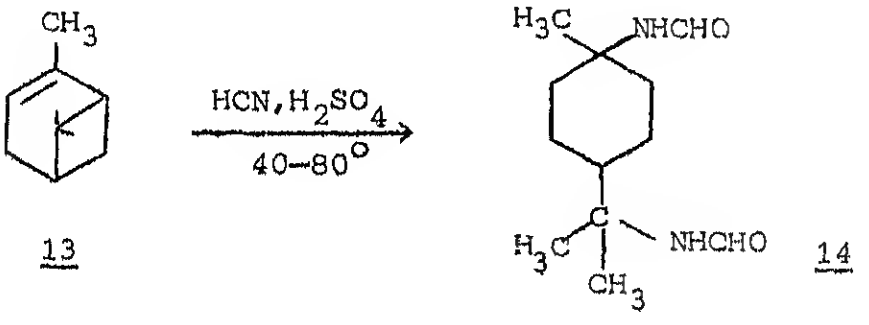
Several other acids, viz., sulphonic acids, phosphoric acids and boron trifluoride, have been used in place of sulphuric acid, in the Ritter reaction. Besides alkenes, the reaction has been extended[5] to a variety of compounds, which serve as carbonium ion source and include alkanes, alkadienes, alicyclic and spiro-alcohols, alkyl chlorides, glycols, aldehydes, chlorohydrins, N-methylolamides, ethers, carboxylic acids, esters, ketones and ketoximes while the alternate source for nitrile component in these reactions is provided by cyanohydrins, cyanoacids and their corresponding esters.

The addition of hydrogen cyanide and nitriles to alkenes has been studied by several investigators.[8-13] There are, however, several reports of products resulting from rearrangement of the incipient carbonium ion.

3-formamido-2,2,3-trimethyl-norcamphane was formed by treating racemic camphene with hydrogen cyanide at 0-3°[14] (Scheme II.4). Rearrangement also occurs with α-pinene giving 1,8-diformamido-p-menthane[13-16].

Scheme II.5



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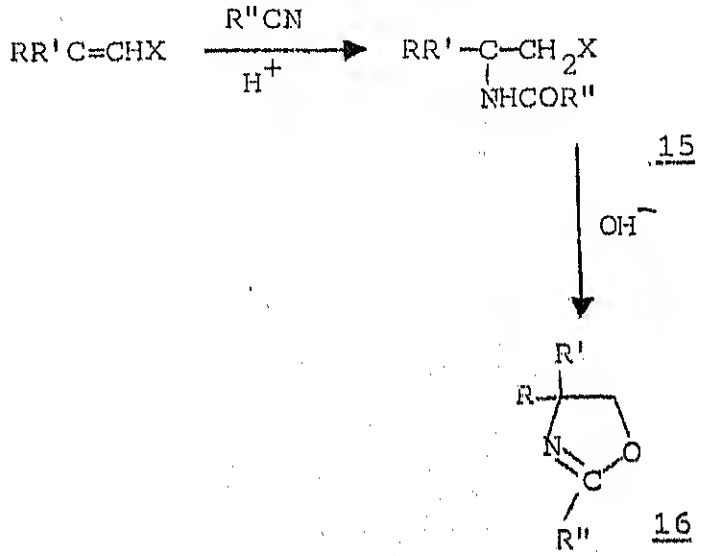
Haloalkenes of the type $R_2C=CHX$ react with nitriles to give N-[2-haloalkyl]amides in good yields. The haloamides were easily dehydrohalogenated to give oxazolines.

Scheme II.6

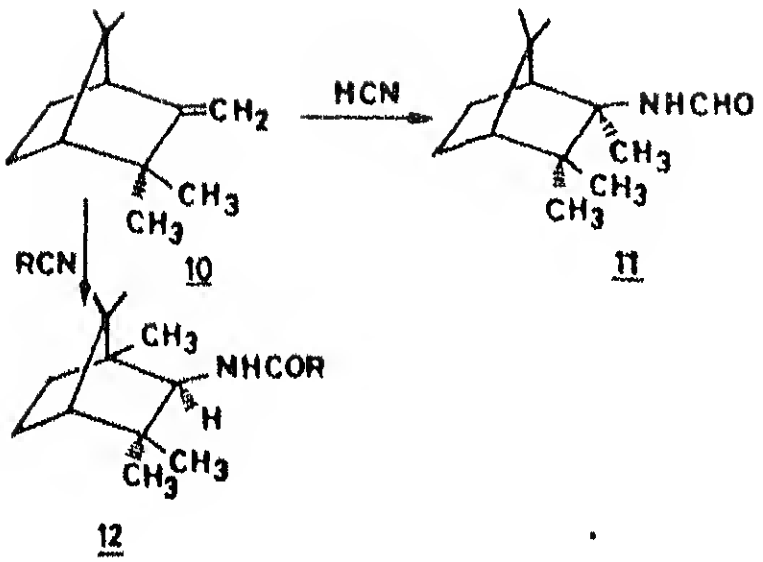


Certain olefinic nitriles undergo unusual intramolecular Ritter reaction, for example, α-cyclopentylidene butyronitrile on heating in presence of polyphosphoric acid produces[17-18] hydrindene (Scheme II.7).

The use of primary, secondary and tertiary alcohols, alicyclic and spiro-alcohols, glycols, heterocyclic alcohols and halohydrines in the Ritter reaction has been investigated.

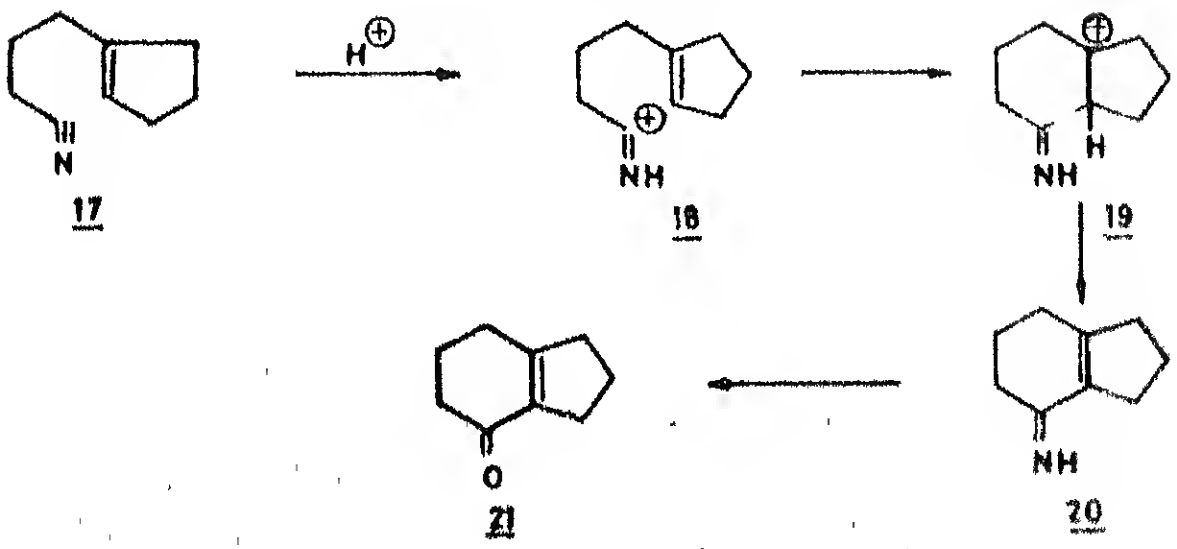
The primary aliphatic alcohols do not react with nitriles, even at elevated temperatures, or on prolonged heating or with fuming sulphuric acid[19]. Other investigators,[20-22] however,

SCHEME II.4



10 11 12

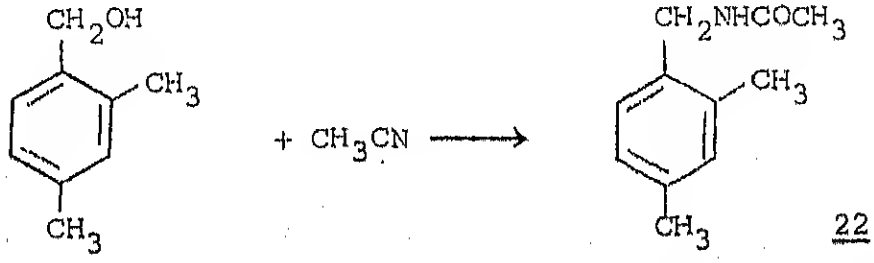
SCHEME II.7



17 18 19 20 21

observed, that primary aralkyl alcohols and glycols condensed smoothly with nitriles under mild conditions to give N-aralkyl amides and N,N'-bis-aralkyl amides in good yields. N-[2,4-dimethyl-benzyl]acetamide was obtained from 2,4-dimethyl-benzyl alcohol and acetonitrile in 87% yield.

Scheme II.8



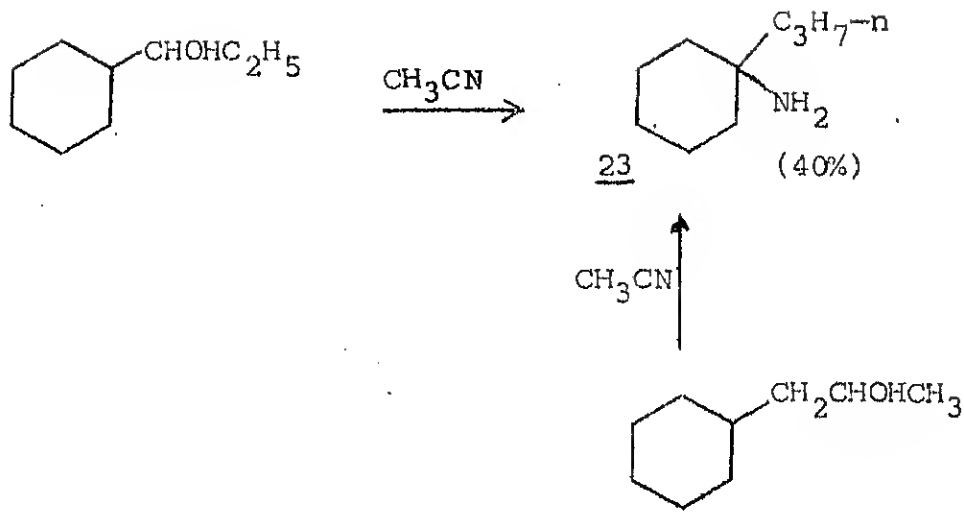
22

An exception to the reactivity of benzyl alcohols is shown by p-nitrobenzyl alcohol, which is inert to nitriles in concentrated sulphuric acid[14]. Glikmans[24] et al. found that alcohols, in general, gave lower yields than the corresponding olefins and required the use of concentrated sulphuric acid.

In a study of the reaction of substituted cycloalkanols it was observed that the yield decreased with the increasing separation of the alcohol function and the substituent.[25]

Similarly, when the ring is further away from the alcohol as in the cyclohexyl propanols, the yields decrease viz., ethyl cyclohexyl carbinol and 1-cyclohexyl-2-propanol give 1-n-propyl-cyclohexyl amine in yields of 40% and 5%, respectively.

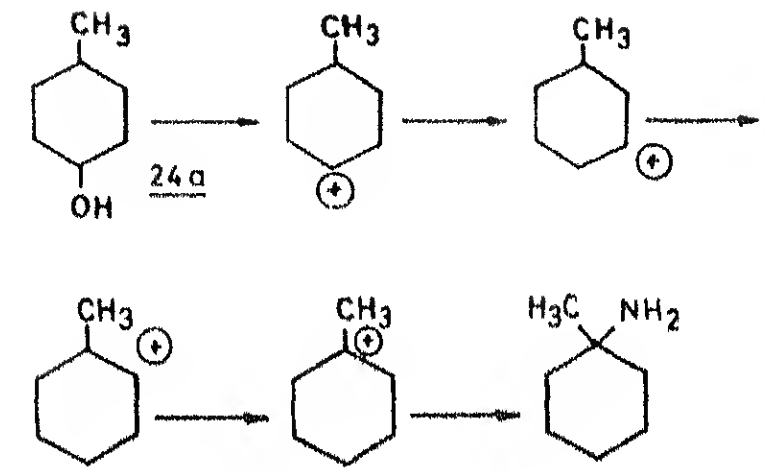
Scheme II.9

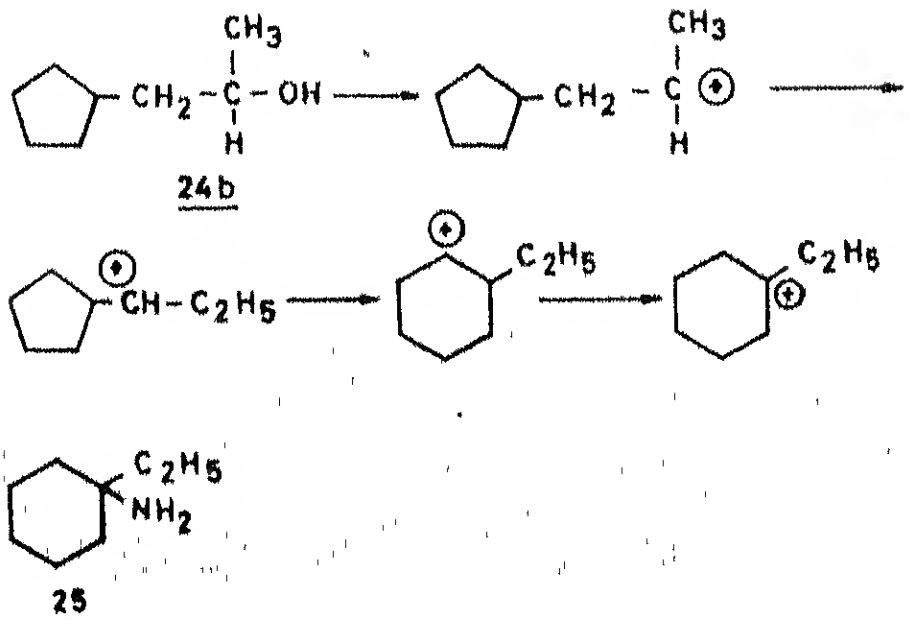


4-methylcyclohexanol and 1-cyclopentyl-2-propanol rearrange involving three transitory carbonium ions in succession to give methyl cyclohexylamine and ethylcyclohexylamine in yields of 5% and 45% respectively (Scheme II.10).

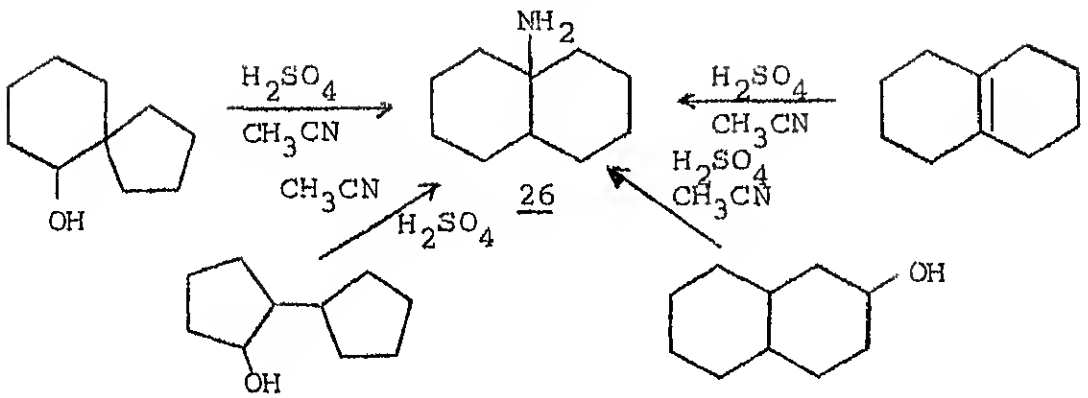
Extending their investigations to alicyclic and spiro-alcohols, christol and coworkers[26-27] found that most Ritter reactions were accompained by a Retropinacol rearrangement. When spiro [4,5]-6-decanol was subjected to the conditions of the Ritter reaction, ring expansion occurred and trans-9-aminodecalin was obtained.

SCHEME II 10


CH3
OH
24a
CH3
CH3
CH3
H3C
NH2


CH3
CH2 – C – OH
H
24b
CH3
CH2 – C
H
CH – C2H5
C2H5
C2H5
C2H5
NH2
25

Scheme II.11



The use of tertiary alkyl halide in place of the corresponding alcohol (in the Ritter reaction) was reported by Magat.[28] A carbonium ion is initially generated by the abstraction of the halogen atom, and then the reaction proceeds as with alcohols. Formic acid as well as sulphuric acid could be employed as reaction media.

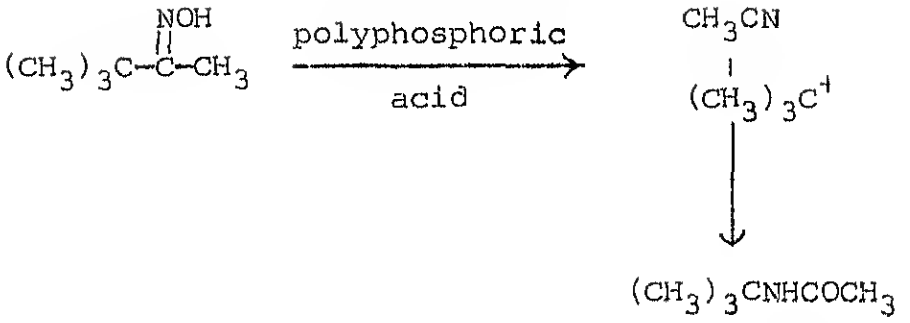
Scheme II.12

$$(CH_3)_3CCl + H^+ \longrightarrow (CH_3)_3C^+ + HCl$$

$$(CH_3)_3C^+ + C_6H_5CN \longrightarrow (CH_3)_3CN{=}C^+C_6H_5$$

While studying the course of the migrating group during the Beckmann rearrangement, Hill[29] and Conley[30-32] discovered that α-trisubstituted and α,α'-tetrasubstituted oximes undergo an initial fragmentation to give an intermediate nitrile and a carbonium ion. The two fragments recombine in a Ritter reaction to form an amide.

Scheme II.13



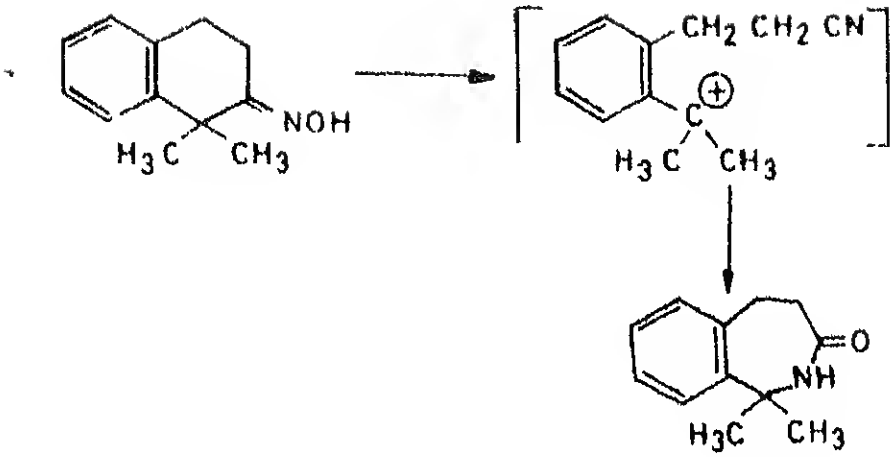
27

In the case of a cyclic ketoxime, fragmentation yielded an unsaturated nitrile which on recombination produced a lactam[30,32-34]. Treatment of 1,1-dimethyl-2-tetralone oxime with hot polyphosphoric acid resulted in the formation of 2-aza-1,1-dimethyl-3-benzosuberone in 24% yield[35] (Scheme II.14).

The facile formation of carbonium ions from t-carboxylic acids and esters of t-alcohols in concentrated sulphuric acid suggested their utilization as carbonium ion sources in the Ritter reaction.

And, indeed treatment of trimethyl acetic acid with hydrogen cyanide in 100% sulphuric acid gave t-butyl amine in 68% yield[25]. Ramp[36] showed that bis(acetoxy methyl) alkylated benzenes could be used as carbonium ion sources. Bis (acetoxymethyl) durene condenses with dinitriles to yield polyamides (Scheme II.15).

SCHEME II 14



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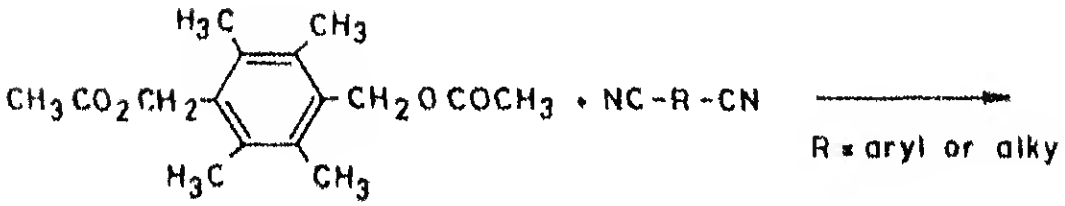
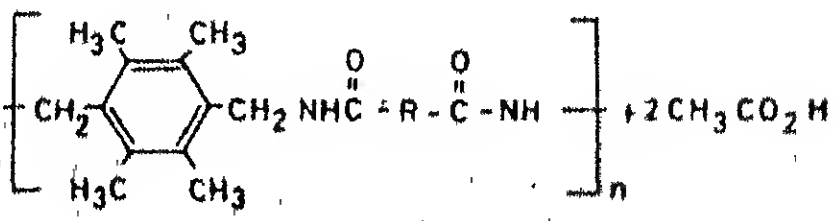
SCHEME II.15





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The preparation of N-benzamide methyl acrylamide[37,38] (yield 83%) has been acnieved by the Ritter action of N-methylol-benzamide and acrylonitrile.

Scheme II.16

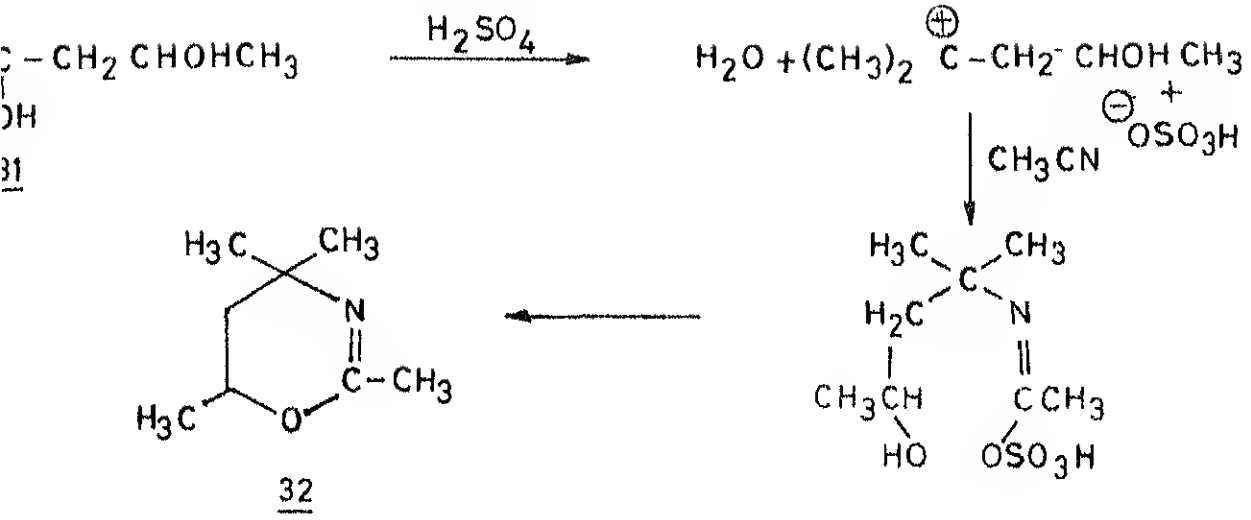
$$C_6H_5\text{-}CONHCH_2OH + CH_2{=}CHCN \longrightarrow \underset{30}{C_6H_5\text{-}CONHCH_2NHCOCH{=}CH_2}$$

Employing the Ritter reaction, a number of heterocyclic systems have been synthesized. This reaction has been successfully used in the preparation of oxazolines[39], pyrrolines[40-41], dihydropyridines[41-42], Δ^2-thiazolines[43-44], thiazines[45-48], isoquinolines[49], 2-quinolones[50], 2-pyridones[51-52], triazines[53], azabicyclo alkanes[54-55], bis(heterocyclyl)alkanes[56] and oxazolones[57].

The synthesis of oxazine from a diol containing both a tertiaryl and a secondary hydroxyl group is illustrated in the Scheme II.17. Treatment of 2-methyl-2,4-pentanediol with acetonitrile gave the 1,3-oxazine in 44% yield (Scheme II.18).

Unsaturated tertiary alcohals are employed for the synthesis of spiroxazines (Scheme II.18). Julia and Papantoniow[39] prepared a series of β-chloroamides from methalloyl cnloride and various nitriles. The amides could be easily

SCHEME II.17



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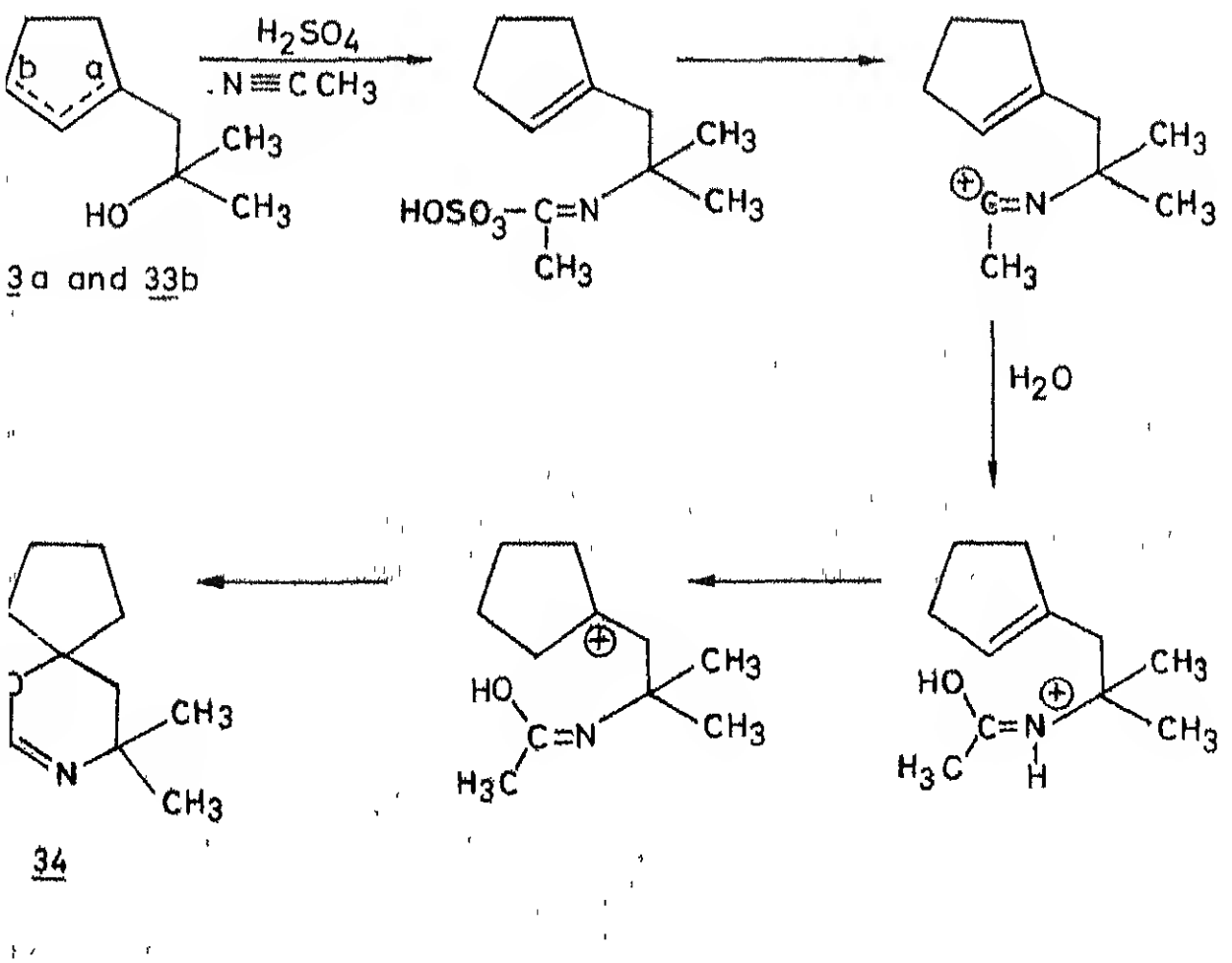
SCHEME II.18

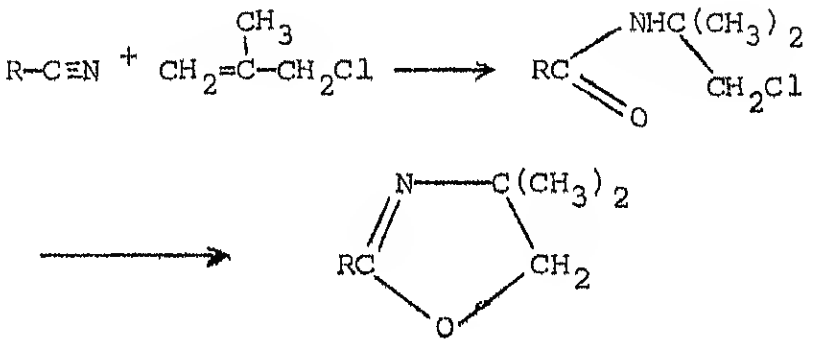


33a and 33b

34

cyclized by either potassium ethoxide or silver fluoroborate to give oxazolines.

Scheme II.19

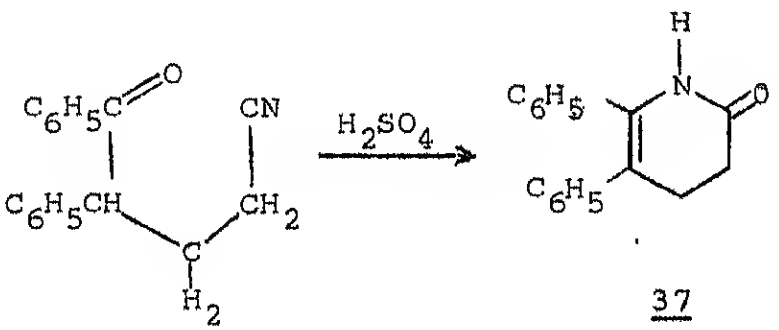


35

A stereospecific synthesis of Δ^2-thiazolines from episulphides has been reported[43-45]. The proposed mechanism for this reaction involves protonation of the episulphide, ring opening by the nucleophilic attack of the nitrile and ring closure to form the thiazoline (Scheme II.20).

The use of keto nitriles in the Ritter reaction provides a direct route to 3,4-dihydro-2-pyridones[51-52] and 2-quinolones[50].

Scheme II.21



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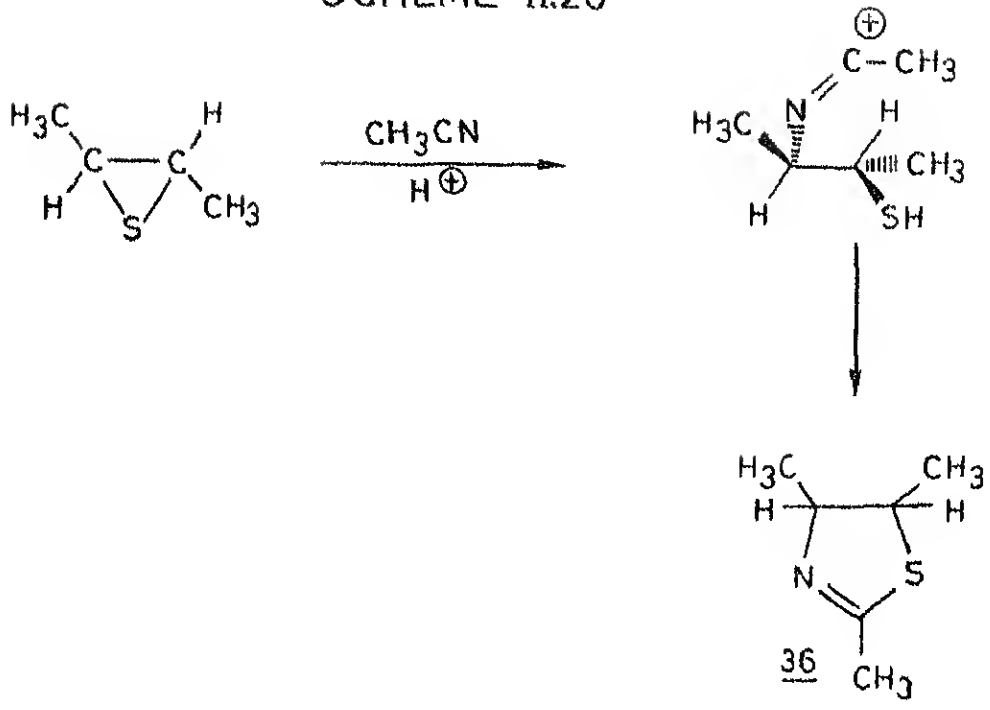
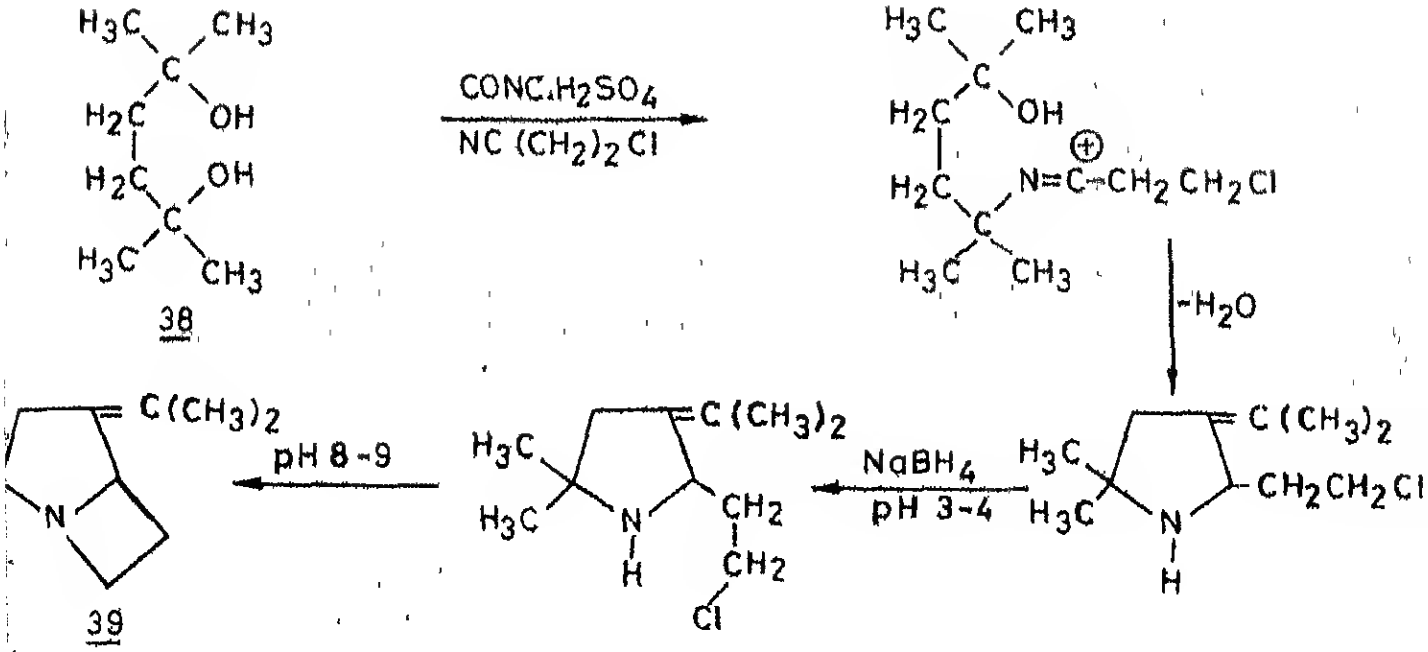
SCHEME II.20



SCHEME II.22

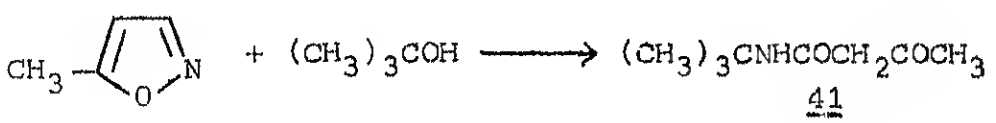


A new approach to the synthesis of polycyclic bases, utilizing the Ritter reaction, was investigated by Meyers and coworkers[54-55]. Treatment of a ditertiary glycol with an ω-chloro nitrile gave rise to an ω-chloroalkyl-1-pyrroline. Subsequent reduction and cyclization *via* intramolecular alkylation yields the 1-azabicycloalkane (Scheme II.22).

The treatment of benzilic acid and benzonitrile with concentrated sulphuric acid gave rise to 2,4,4-triphenyl-5-oxazolone[57], involving the participation of $(C_6H_5)_2\overset{+}{C}COOH$ cation (Scheme II.23).

Eugster and coworkers employed 5-methyl and 5-phenyl-isoxazole in an unusual extension of the Ritter reaction. Under acid conditions these compounds behave as cyanoacetones and give the corresponding Ritter products. The reaction of 5-methyl-isoxazole with *t*-butyl alcohol yields N-*t*-butylaceto acetamide.

Scheme II.24



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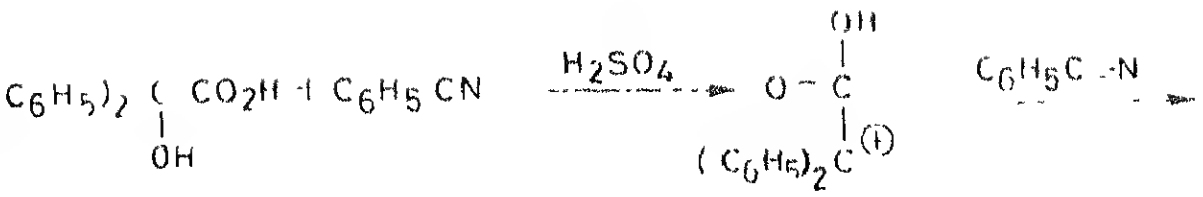
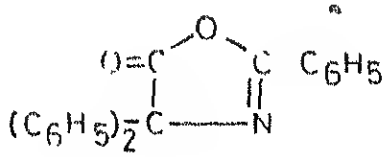
With α,β-unsaturated ketones, the isoxazole forms 5,6-dihydro-2-pyridones (Scheme II.25).

SCHEME II.23





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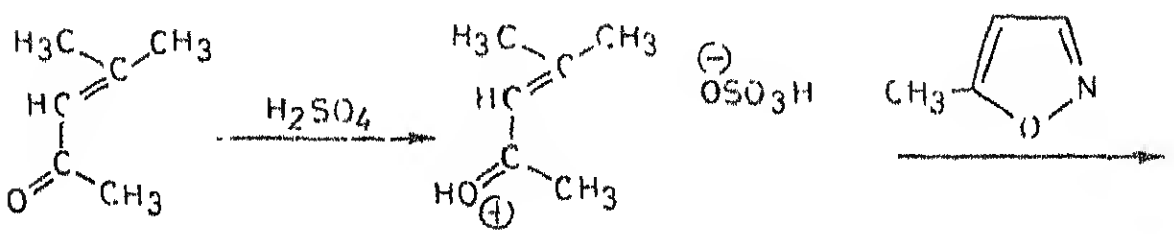
SCHEME II.25



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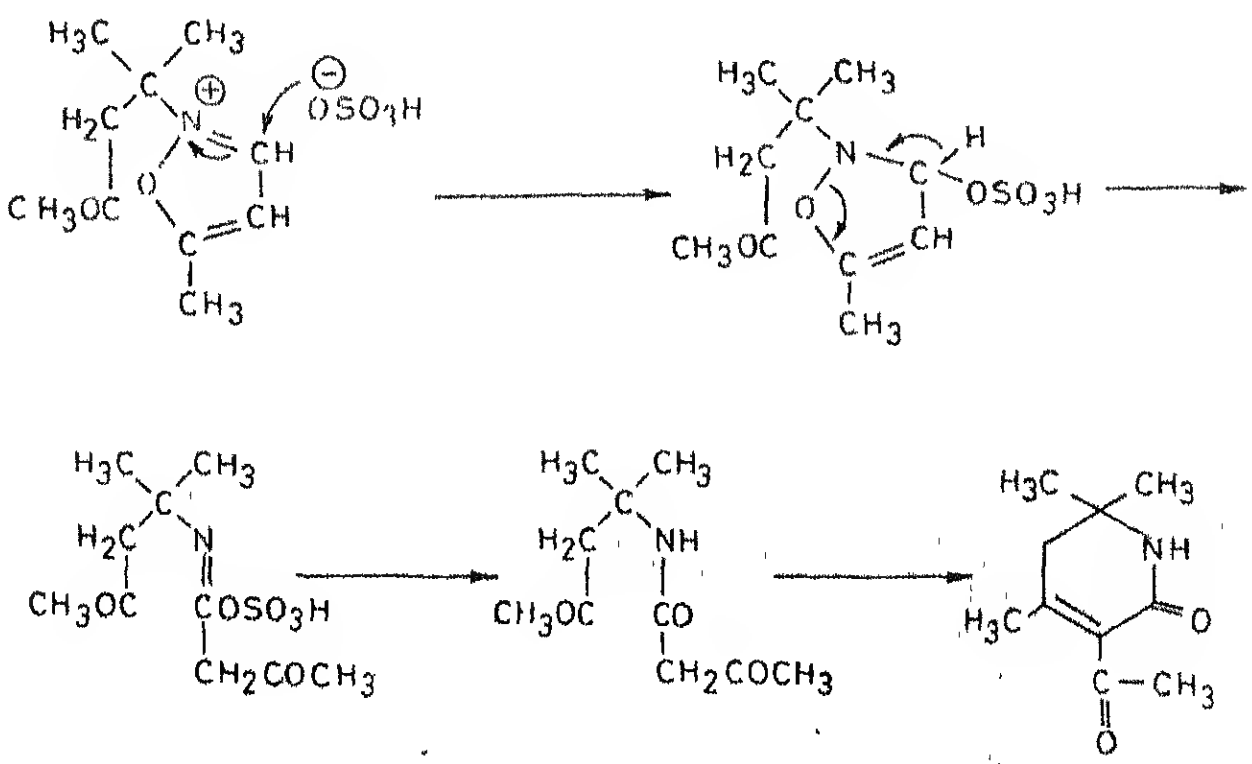
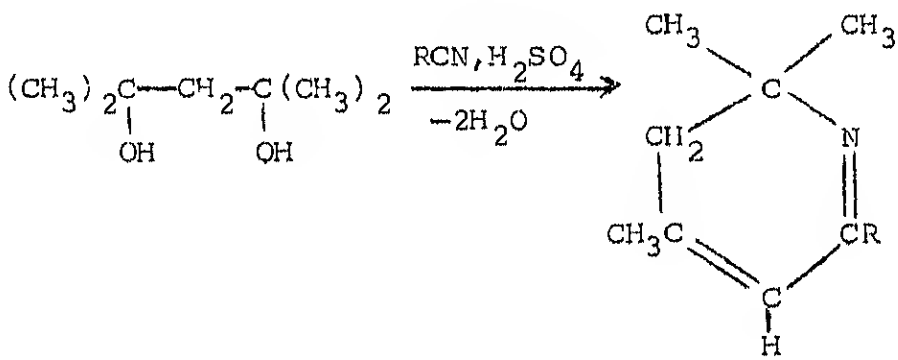


A series of 1-pyrrolines (yield 60-80%) were prepared by heating 1,4-diols with various nitriles. Under the same conditions, however, 2,5-dimethyl-hexadiene gave the corresponding pyroline. As a consequence of a competing polymerisation, replacement of the 1,4-diols (vide supra) by 1,3-diol-2,4-dimethyl-pentane-2,4-diol permits the preparation of a variety of 5,6-dihydropyridines. The yields are considerably lower (~20%) because of the cleavage of the diol to acetone and isobutene.

From the 1,3-diol and acetonitrile the N-t-butylacetamide was isolated in 50-55% yield.

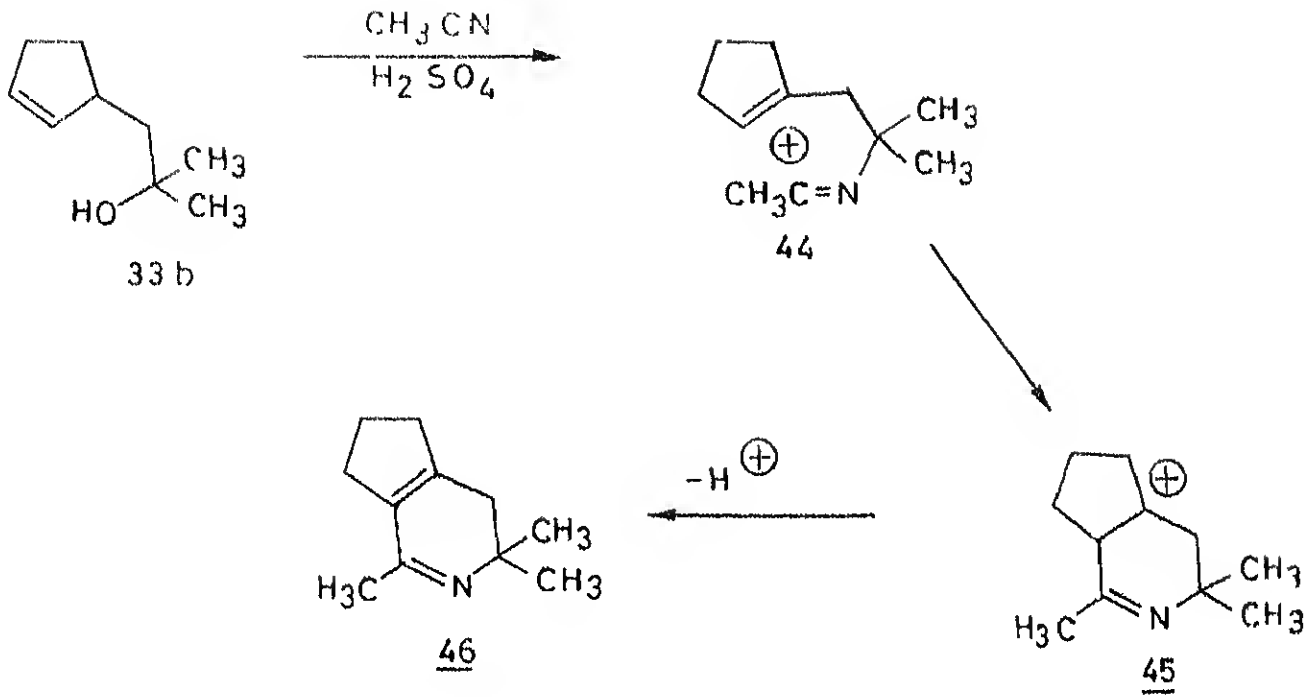
Scheme II.26



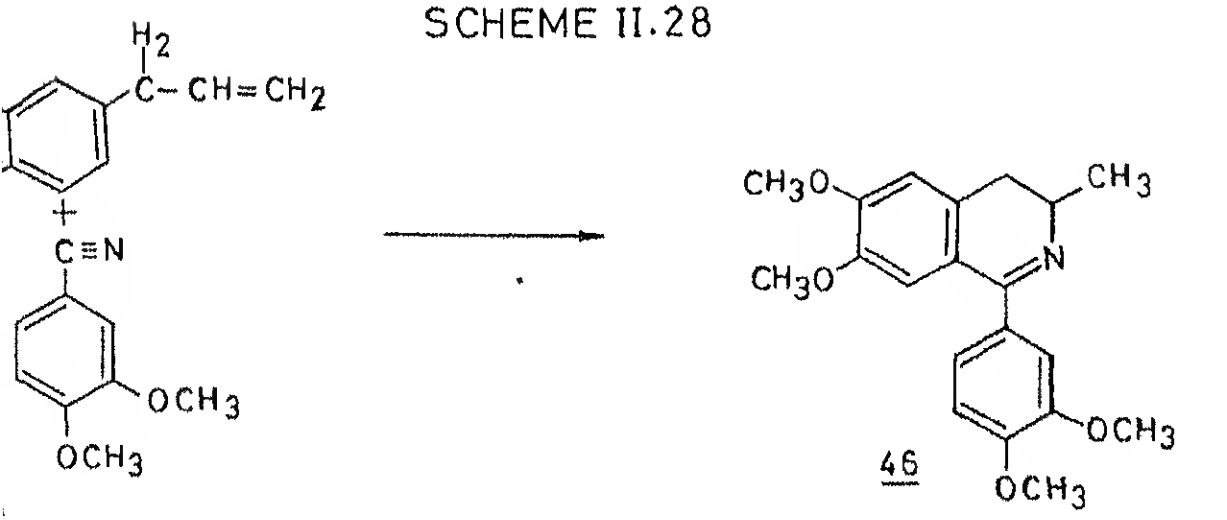
44

Treatment of α-(3-cyclopentenyl)-t-butyl alcohol with acetonitrile in sulphuric acid (concentrations above 93%) led to an azocarbonium ion that lost a proton to give 3,4-cyclopenteno-5,6-dihydropyridine[41-42].

SCHEME II 27



SCHEME II.28

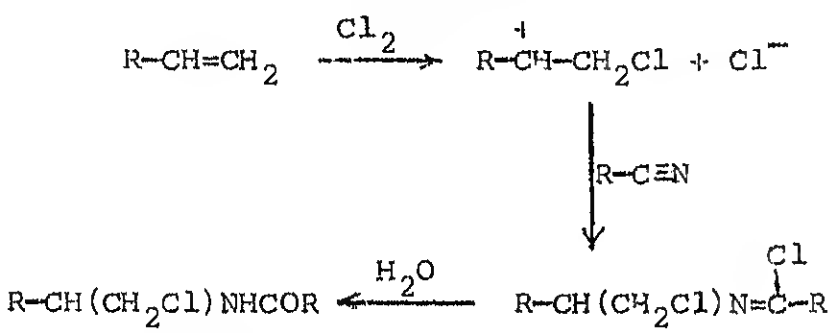


SCHEME II.30

3,4-dihydroisoquinolines[49] have been obtained by the reaction of methyleugenol with alkoxyaryl nitriles and of isosafrol or methylisoeugenol with a variety of nitriles. Veratronitrile and methyleugenol give 1-(3',4'-dimethoxyphenyl)-3-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline in 53% yield (Scheme II.28).

Cairns and his coworkers[58] have demonstrated the formation of imidoyl chloride, produced in the reaction of chlorine with an olefin in the presence of an alkyl/aryl nitrile, which undergoes smooth hydrolysis to yield N-[2-chloroalkyl]amide (Scheme II.29). Haloalkylamines were obtained when HCN was used as a nitrile source. Theilacker[59] has reported a comparable reaction, which involves the reaction of hypochlorous acid and cyclohexene in the presence of aqueous acetonitrile (solvent) (Scheme II.30).

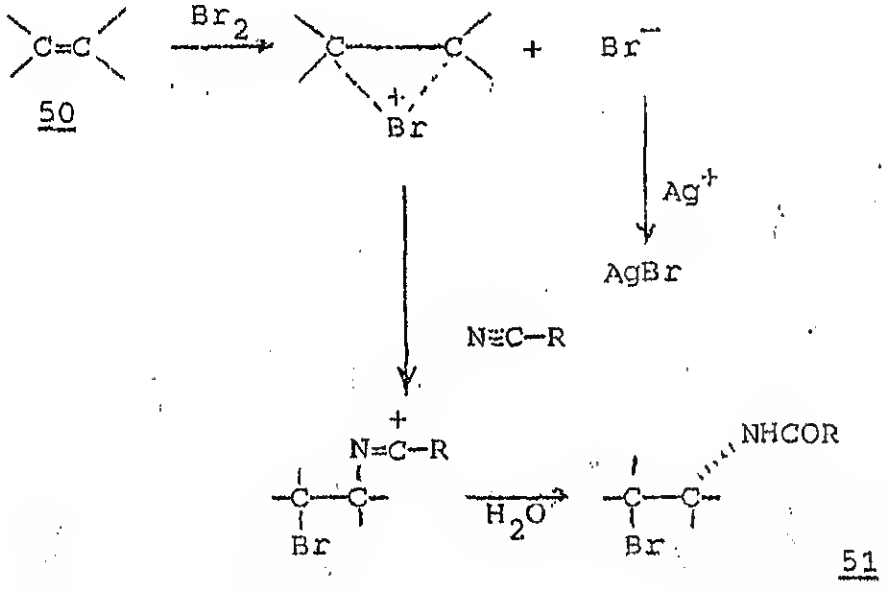
Scheme II.29



48

Likewise, bromine has been found to be useful for the generation of carbonium ion in the Ritter reaction, the bromonium ion thus produced, undergoes cleavage by the attack of the nitrile group in a stereospecific manner. The success of the reaction, however, depends upon the simultaneous removal of bromide ions present in the solution.(Scheme II.31).

Scheme II.31



50 51

Amino selenation of olefins has been achieved by the reaction of phenyl selenyl chloride with olefins and acetonitrile, in the presence of an acid catalyst[60].

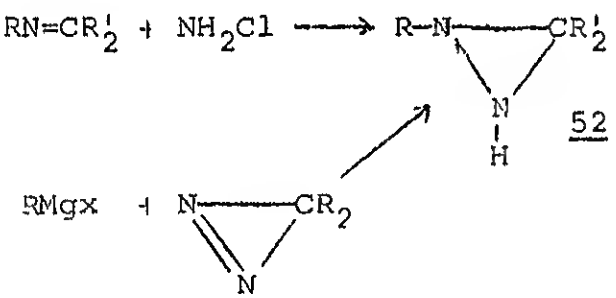
It has been reported that carbon monoxide can successfully replace the nitrile in Ritter reaction (involving an olefin) with the formation of a carboxylic acid. This modified reaction is often referred to as Koch-Hoff reaction.[61,62]

At the outset, it would be desirable to briefly review the various methods available for the synthesis of diaziridines, hydrazones, imidines and oxaziridines.

Diaziridines

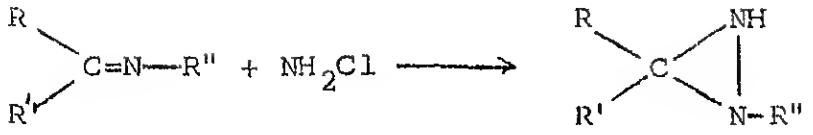
N-substituted diaziridines are prepared by the reaction of chloramine with ketimines[63-64]. The same diaziridine can also be obtained by addition of Grignard reagents to diazirines.[63]

Scheme II.32



Schmitz and Habisch[63] investigated the action of chloramine on simple schiff's bases. In the aliphatic series, diaziridine formation was observed in all the cases investigated. Ethereal solutions of chloramine are reported to react with Schiff's bases, at room temperature, within few hours, as shown in Scheme II.33.

Scheme II.33



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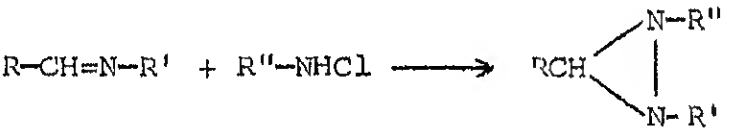
The reactions of chloramine are not generally successful with N-chloroalkylamines. Therefore, it was surprising that the diaziridine synthesis occurred smoothly from aliphatic Schiff's bases and N-chloroalkylamines.[66]

Scheme II.34

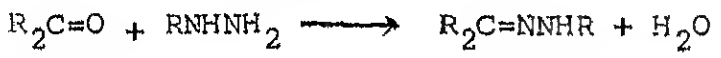


54

Hydrazones

Hydrazones are generally prepared from ketone or aldehydes and the appropriate hydrazine[67].

SchemeII.35



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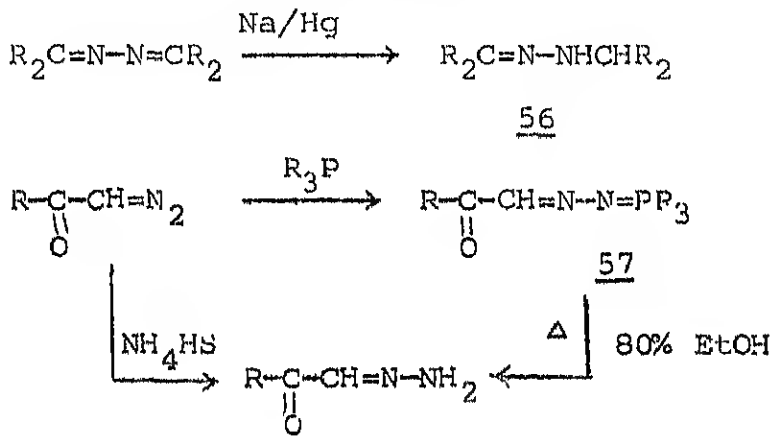
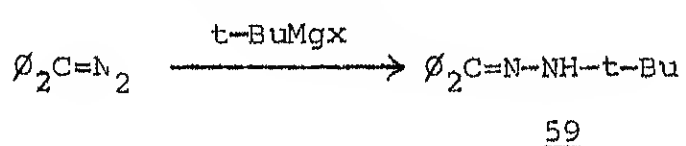
Hydrazones have been prepared reductively from azines, with the use of sodium amalgam, and from α-diazoketones[68-70] with the use of either phosphines or ammonium hydrosulphide, (vide scheme II.36).

Scheme II.36



The addition of Grignard reagents to either azines[71-73] or diazo compounds gives high yield of hydrazones, (vide Scheme II.37).

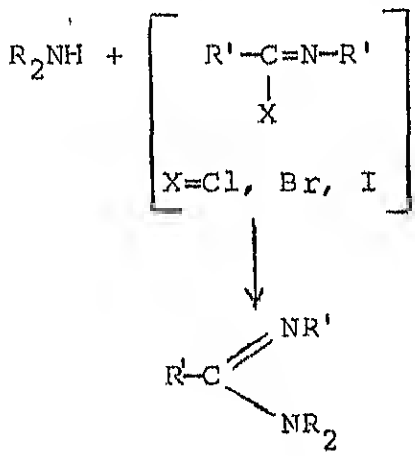
Scheme II.37



Amidines

The amidines are prepared by the solvolysis of thioamides,[74-75] imidoyl halides, sulphonates, chlorophosphonate imidate[74] and thioimidate[75] esters with ammonia or amines. A illustrative example is depicted in Scheme II.38.

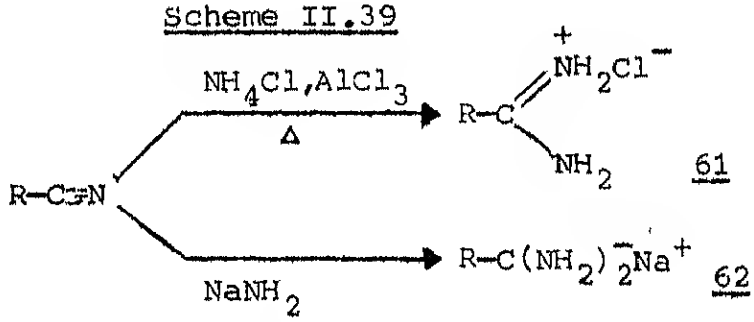
Scheme II.38



60

A more limited method in the addition of ammonia or am to nitriles, which is achieved by acid catalysis[76a-b] (heatin with ammonia and ammonium salts under pressure) and base cata (sodium amide).[76c]

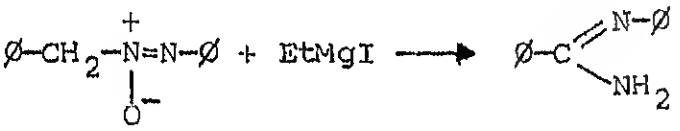
Scheme II.39



The pyrolysis of amides[77] and of imidate esters, and the base catalysed rearrangement of hydrazones[78], gave variable quantities of amidines.

Alternatively, amidines can be prepared by the reaction of azoxy compound with Grignard reagent (vide Scheme II.40).

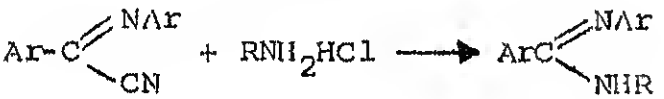
Scheme II.40



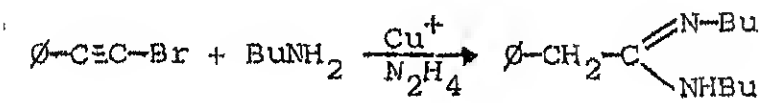
63

Amidines have also been prepared by the cleavage of α-imino nitriles with amine salts[80a], and the solvolysis of bromoacetylenes, ortho esters or thio esters with amines[80c] (vide Scheme II.41).

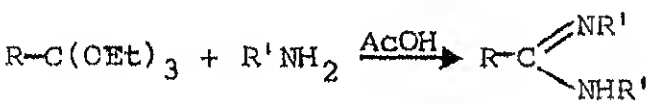
Scheme II.41



64



65



66

Oxaziranes

Oxaziranes are produced by the action of peracids on Schiff's bases as shown in (Scheme II.42).

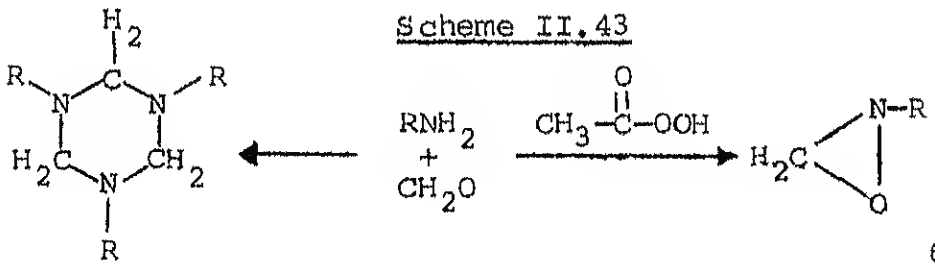
Scheme II.42

R=H, R'=H, R"=t-Bu

67

It is not always necessary to use a preformed base. Alternatively a carbonyl compound and the amine are taken together in an inert solvent, followed by the addition of per acid. The synthesis of 2-cyclohexyl-oxazirane[83] proceeded in 66% yield, from cyclohexylamine, formaldehyde and peracetic acid as shown in Scheme II.43.

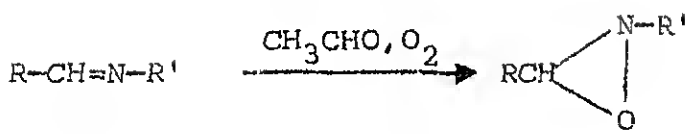
Scheme II.43



68

A further simplication in the reaction conditions is possible by the in situ generation of peracid by the aerial oxidation of an aldehyde (vide infra).

Scheme II.44



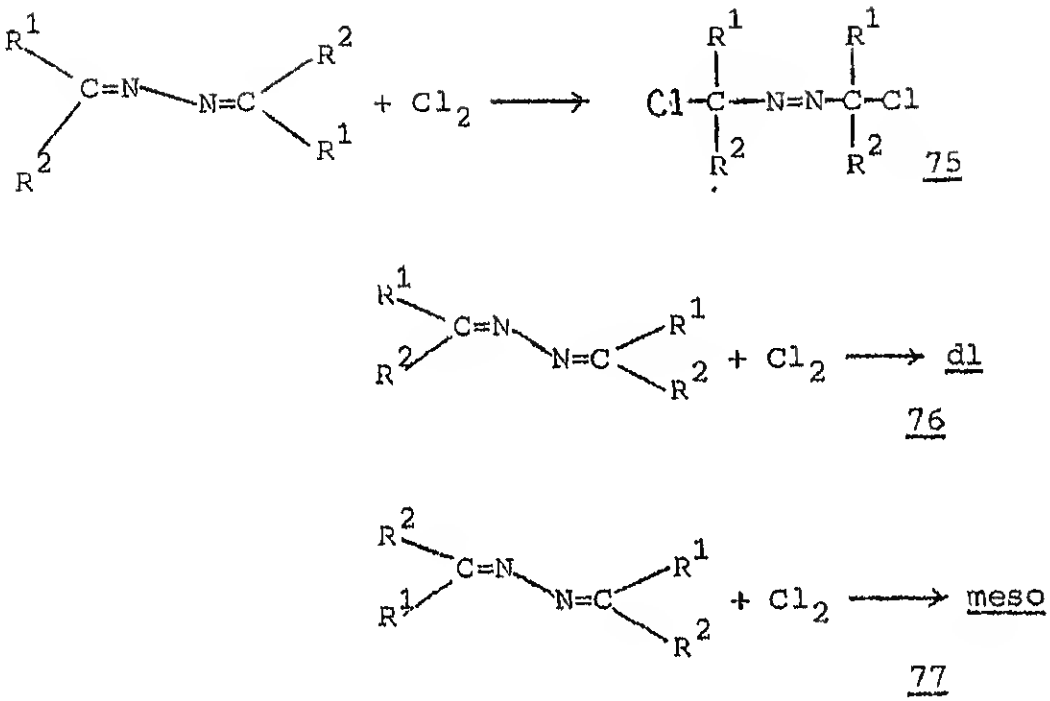
69 70

Compounds containing two oxazirane rings are obtainable from Schiff's bases of glyoxal or terephthalic dialdehyde[84]. A bifunctional oxazirane is obtained from ethylene-diamine and cyclohexanone (Scheme II.45).

Below and Person[84] obtained an oxazirane by the reaction of ozone on isobutylidene tert-butylamine (Scheme II.46). Oxazirane rings are also formed by the action of silver oxide on perhydro nitrogen heterocycles (Scheme II.47).

The 1,4-addition of chlorine to Ketazines,[85] in dichloromethane at -60°, is shown by nmr, to proceed stereospecifically. Thus, symmetric (syn, syn or, anti, anti) Ketazine isomers give meso- α- α'-dichloro azoalkanes and unsymmetric (syn, anti) Ketazine isomers give the dl product (vide Scheme II.48).

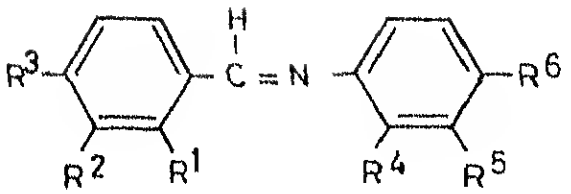
Scheme II.48



RESULTS AND DISCUSSION

The reaction of Schiff's bases (78a-c) with sulphuryl chloride in acetonitrile took place smoothly giving rise to corresponding benzaldehyde-phenyl-hydrazones (87a-c) respectively. Reaction of Schiff's bases (78d-m) with sulphuryl chloride in acetonitrile yielded the corresponding N-phenyl-benzimidines (85d-m) respectively. Here the chloronium ion, formed by the addition of chlorine to the C=N double bond of a Schiff's base, is attacked by the nitrile funotion, leading to the generation

SCHEME II.49



78 a-m

a : R^3= Br , R^1= R^2= R^4= R^5= R^6= H

b : R^3= R^6= Cl , R^1 = R^2 = R^4= R^5 = H

c : R^1= R^2= R^3= R^4= R^5= R^6= H

d : R^3= Cl , R^1 = R^2= R^4 = R^5= R^6 = H

e : R^6= Cl , R^1 = R^2 = R^3 = R^4= R^5 = H

f : R^6= NO_2, R^1 = R^2 = R^3 = R^4 = R^5 = H

g : R^3= R^6 = NO_2, R^1 = R^2 = R^3 = R^4 = H

h : R^3 = R^5 = NO_2, R^1 = R^2 = R^4 = R^6 = H

i : R^3 = R^4 = NO_2, R^1 = R^2 = R^5 = R^6 = H

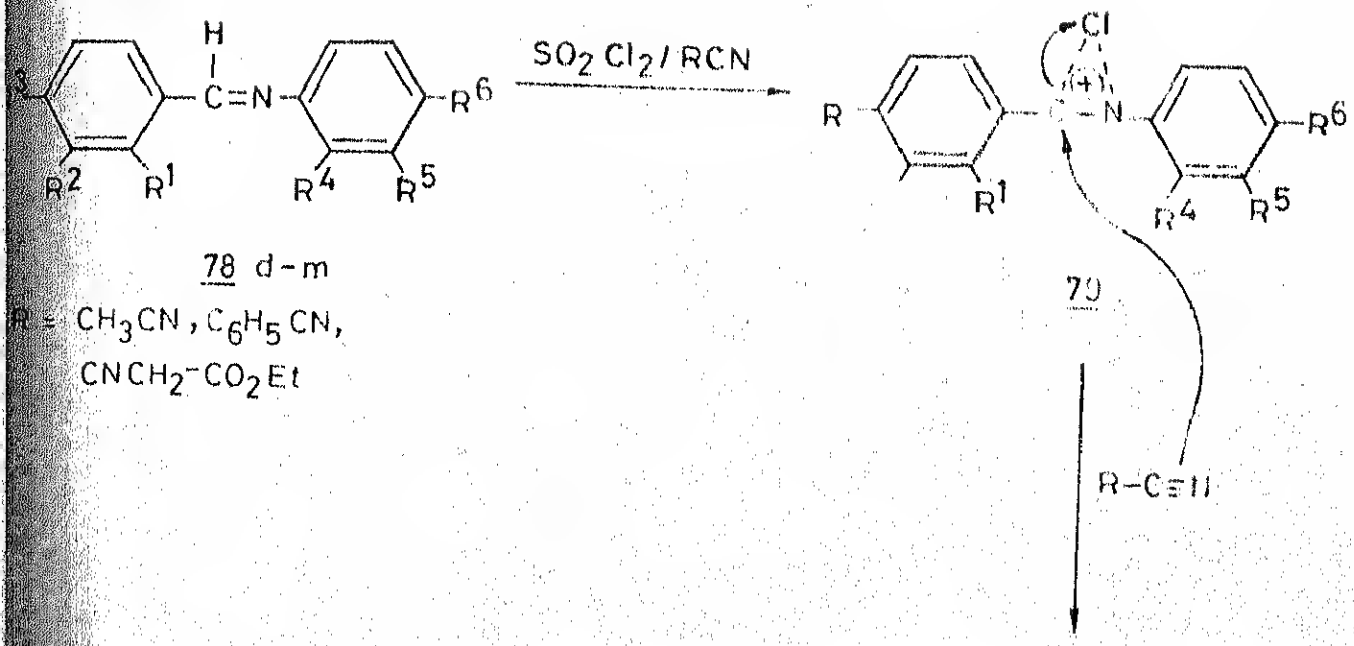
j : R^5= NO_2, R^1 = R^2 = R^3 = R^4 = R^6 = H

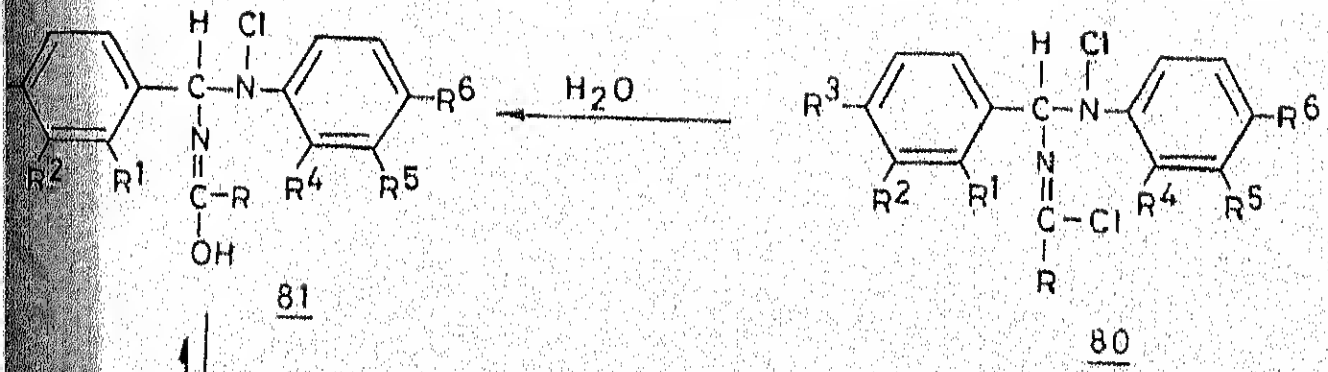
k : R^4 = NO_2, R^1 = R^2 = R^3 = R^5 = R^6 = H

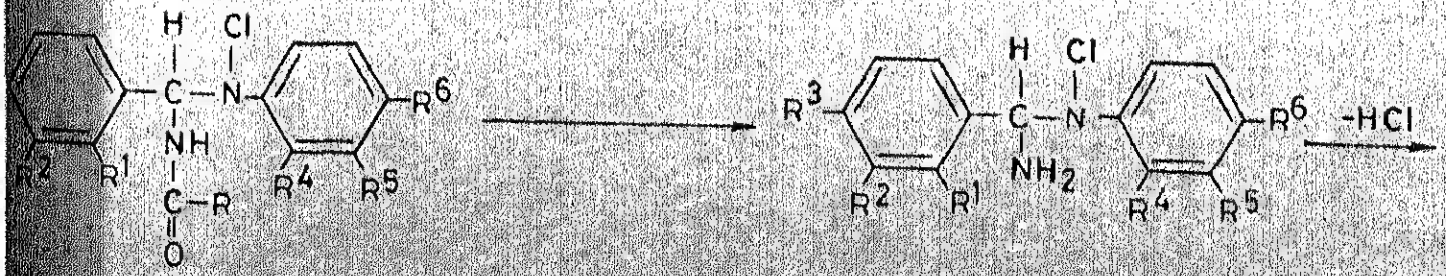
l : R^3= Br, R^6 = NO_2, R^1 = R^2 = R^3 = R^4 = H

m: R^2 R^3 = OCH_3 , R^5 = NO_2, R^1 = R^4 = R^6 = H

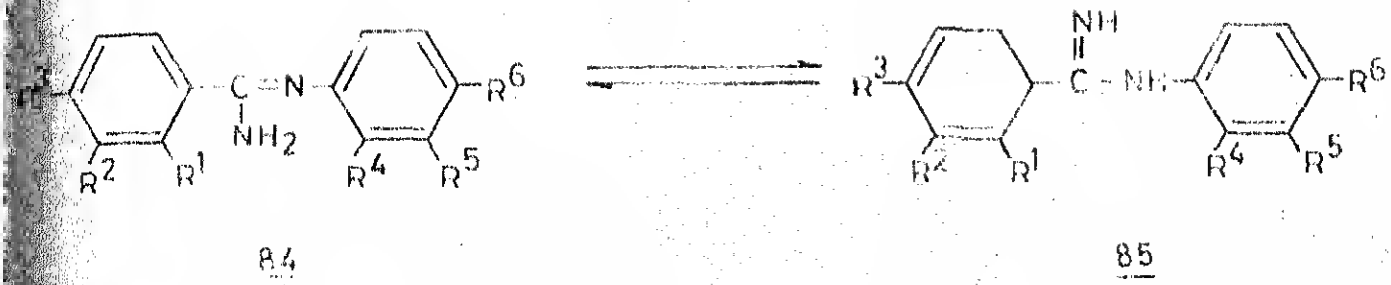
Contd.


SO2 Cl2 / RCN
78 d-m
R = CH3CN, C6H5CN,
CNCH2-CO2Et
79
R-C≡N

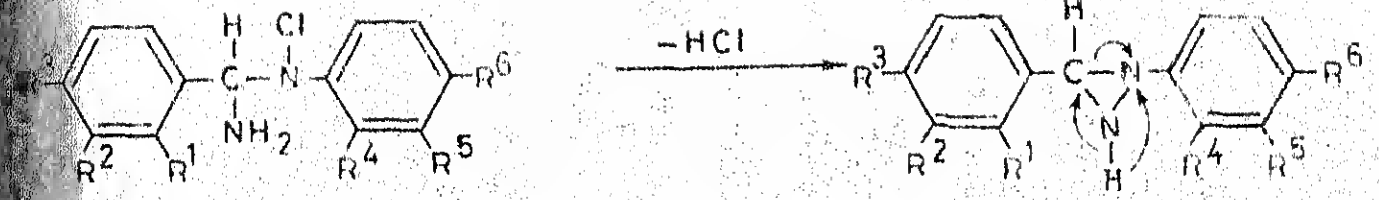

H2O
81
80


-HCl
82
83

Contd.

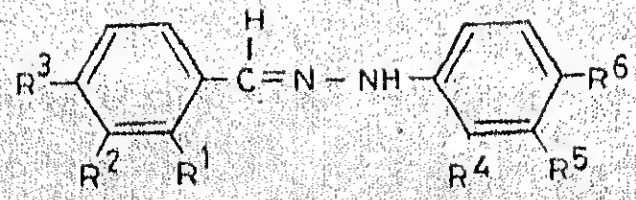


84 ⇌ 85



83 a-c

86



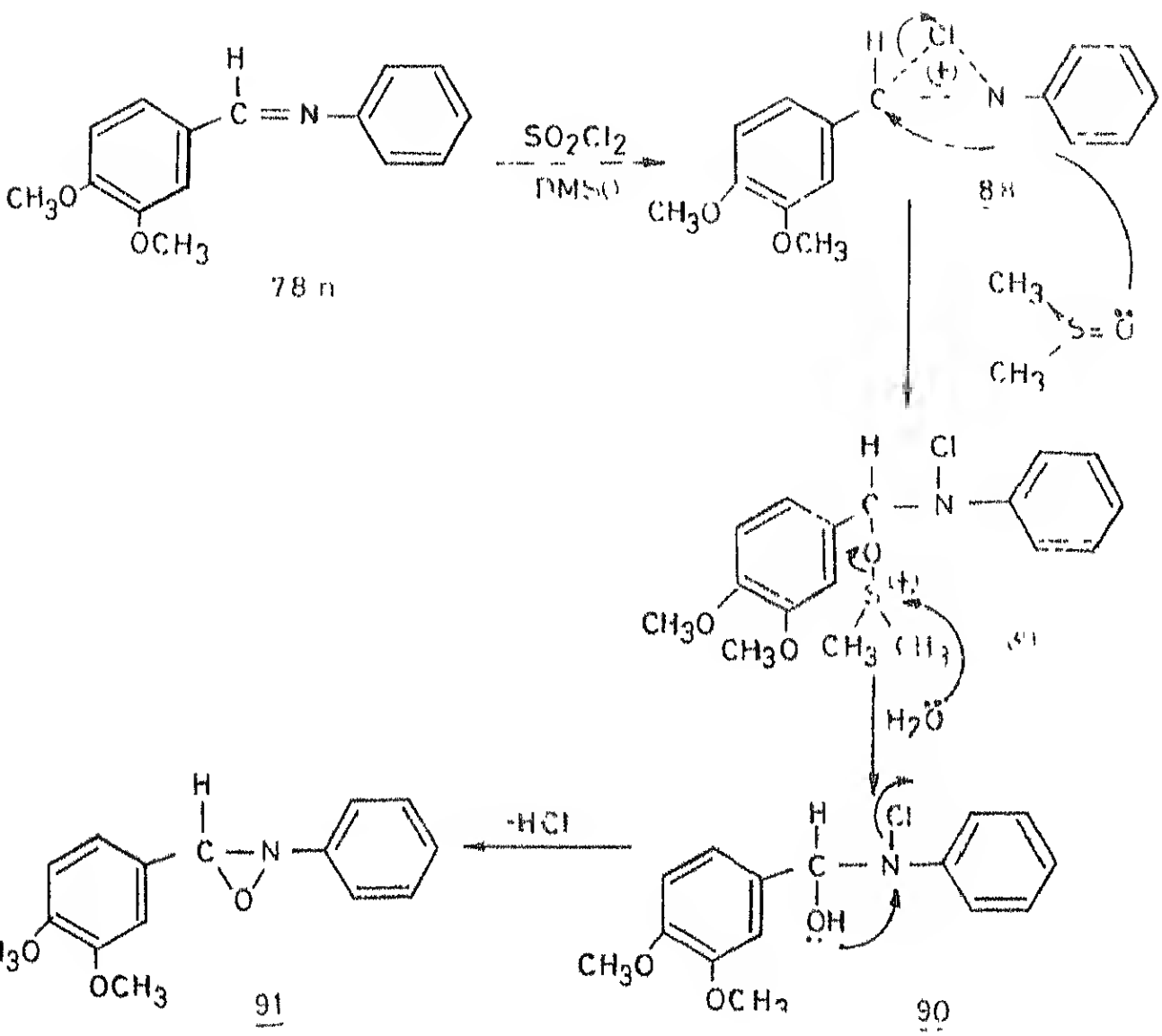
87

of imidoyl chloride (80) (Scheme II.49), which gets readily hydrolysed by adding water to give the corresponding amine. The amine (83) leads to the formation of two products, viz., N-phenyl-benzimidines and phenylhydrazones. The latter compounds are formed via the corresponding diaziridine intermediates (Scheme II.49). Reaction of Schiff's bases (78n-r) with sulphuryl chloride in acetonitrile gave rise to the corresponding benzanilides, as shown in Scheme I.51. Apparently the nitrile function does not participate in the reaction.

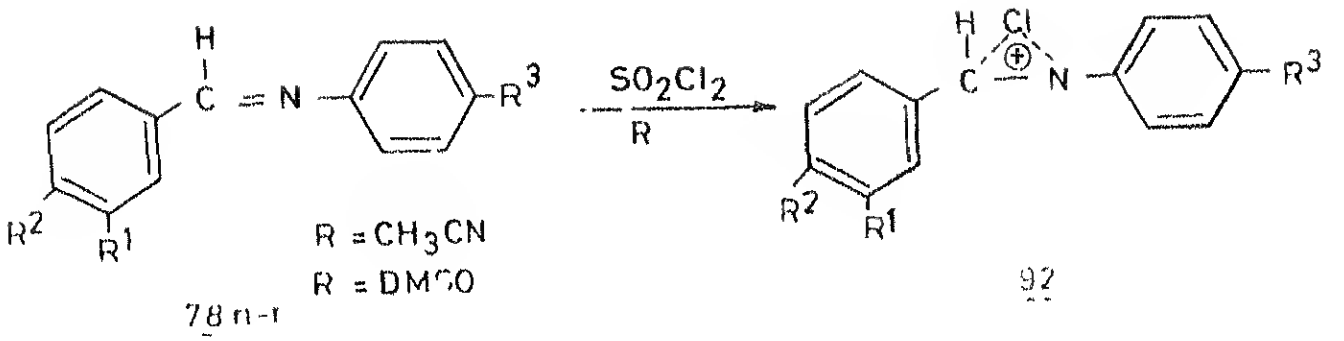
The same products, viz., benzanilides (95o,p,q) were isolated, if acetonitrile is replaced by DMSO, in the above reaction. However, in the reaction of N-[3,4-dimethoxy-benzylidene]-aniline with SO_2Cl_2-DMSO, the corresponding oxaziridine derivative (91o) was obtained. The formation of the latter compound has been rationalized as depicted in Scheme II.50, and illustrates, for the first time the participation of DMSO in the Ritter reaction.

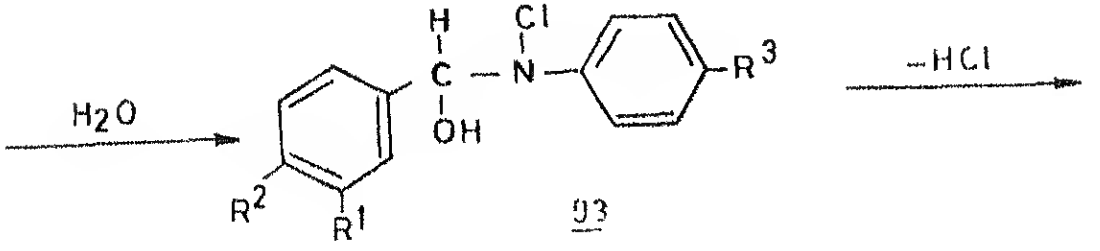
Reaction of Schiff's bases (78d-g) with sulphuryl chloride in ethyl cyanoacetate also afforded the corresponding N-phenyl-benzimidines. Here the chloronium ion, formed by the addition of chlorine to the C=N double bond of the Schiff's base, is attacked by the nitrile function of ethyl-cyano-acetate (Scheme II.49). This leads to the generation of imidoyl-chloride which gets readily hydrolysed to give the corresponding amine. The

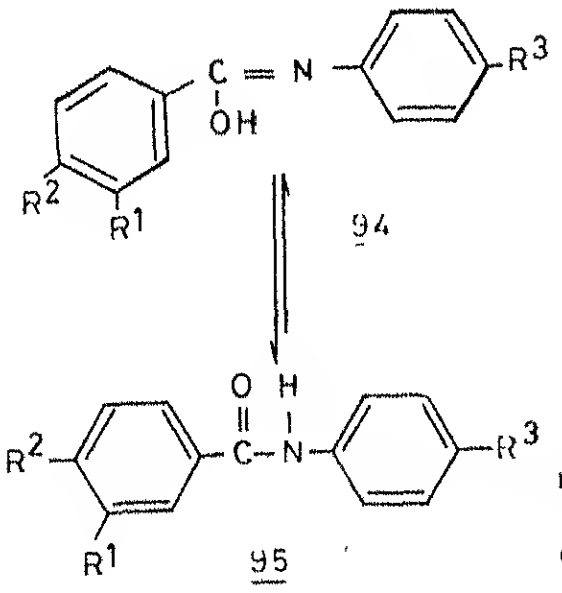
SCHEME II 50



SCHEME II.51







n, $R^1 = R^2 = OCH_3$, $R^3 = H$

o, $R^1 = R^2 = OCH_3$, $R^3 = Cl$

p, $R^1 = OCH_3$, $R^1 = R^2 = H$

q, $R^1 = OCH_3$, $R^2 = H$, $R^3 = Cl$

r, $R^1 = R^2 = R^3 = OCH_3$

latter compound loses a molecule of HCl, leading to the formation of the corresponding N-phenylbenzamidines (Scheme II.49).

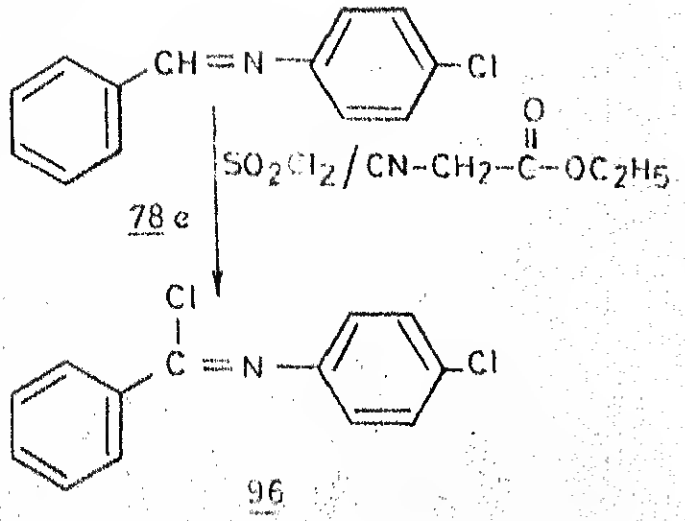
Aldazines (97a-f) on treatment with SO_2Cl_2-CH_3CN gave rise to the corresponding α-chloroaldazines (98a-f) as shown in Scheme II.53.

Reaction of N-[benzylidene]-p-chloro-aniline (78e) with sulphuryl chloride in ethyl-cyanoacetate also yielded the corresponding benzimid chloride (96e) as shown in Scheme II.52. In both the cases, cited above, nitrile function (viz., CH_3CN and $CNCH_2CO_2Et$) apparently did not participate in the reaction (Scheme II.52 and II.53). (87a-c) are known compounds. These were synthesized by employing modified Ritter reaction using SO_2Cl_2-CH_3CN/C_6H_5CN and Schiff's bases. These compounds were characterized on the basis of physical data, shown in the following table.

On the basis of elemental analysis (85d) corresponded to molecular formula $C_{13}H_{11}ClN_2$. It gave a peak at m/e, 215, (M^+-NH) in in the mass spectrum (Fig. II.3). It showed IR absorption maxima at 3340, 3460(ν_{NH}), 1620, 1590($\nu_{C=N}$) (Fig. II.1). It gave PMR signals at δ 5.0(s, 1H, NH, exchangeable with D_2O), 6.5-7.7 (m, 8H, aromatic + 1H, NH) (Fig. II.2). It was identified as 85d.

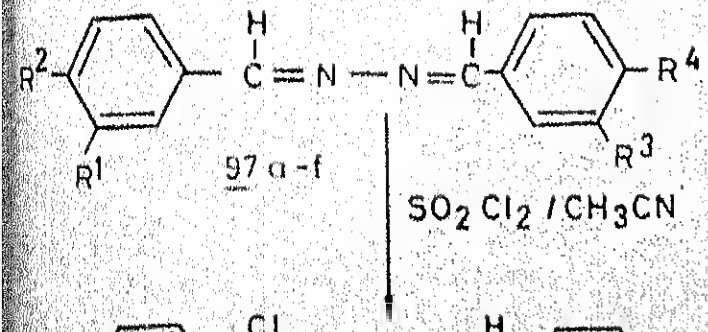
On the basis of elemental analysis 96e corresponded to molecular formula $C_{13}H_9Cl_2N$. It gave a peak at m/e, 215, (M^+-Cl) (Fig. II.9) in the mass spectrum. It exhibited IR absorption maxima,

SCHEME II.52



96

SCHEME II.53



98

a , $R^1 = R^2 = R^3 = R^4 = H$

b , $R^1 = R^2 = R^3 = R^4 = OCH_3$

c , $R^1 = R^3 = H$, $R^2 = R^4 = Cl$

d , $R^1 = R^3 = H$, $R^2 = R^4 = NO_2$

e , $R^1 = R^3 = H$, $R^2 = R^4 = Br$

f , $R^1 = R^3 = H$, $R^2 = R^4 = OCH_3$

TABLE-1

Compd.	m.p. °C (lit.)	Mol. Formula	M^+ (70 eV)	IR (KBr) cm^{-1}	^1H NMR
p-Bromo-benzadehyde-N-phenyl hydrozone	170(170)	$C_{13}H_{11}BrN_2$	275,157, 92,77	3300(ν_{NH}) 1600($\nu_{C=N}$)	4.9(s,1H,NH), 6.4-7.4(m, 9H,aromatic +1H,CH), olefinic
p-Chloro benzal-dehyde N-p-chloro phenyl hydrazone	122(120)	$C_{13}H_{10}Cl_2N_2$	264,122, 126	3350(ν_{NH}) 1595($\nu_{C=N}$)	5.0(s,1H, NH) exchange-able with D_2O, 6.5-7.4 (m,8H,aro-matic +1H,CH) olefinic
Benzal-dehyde phenyl hydrazone	159(161)	$C_{13}H_{12}N_2$	196,92, 77	3360(ν_{NH}), 1590($\nu_{C=N}$)	4.8(s,1H,NH) exchangeable with D_2O, 6.4-7.0(m, 10H,aromatic + 1H,CH), olefinic

1615($\nu_{C=N}$),1460,1260 cm^{-1}. It gave PMR signal at δ5.8-7.1 (m, 8H, atomatic). It was identified as 96e.

N-[benzylidene]-p-nitroaniline on treatment with sulphuryl chloride in acetonitrile furnished, a compound which analysed for $C_{13}H_{11}N_3O_2$. It gave molecular ion peak at 241, in the mass spectrum. It exhibited IR absorption bands at 3320, 3460(ν_{NH}),

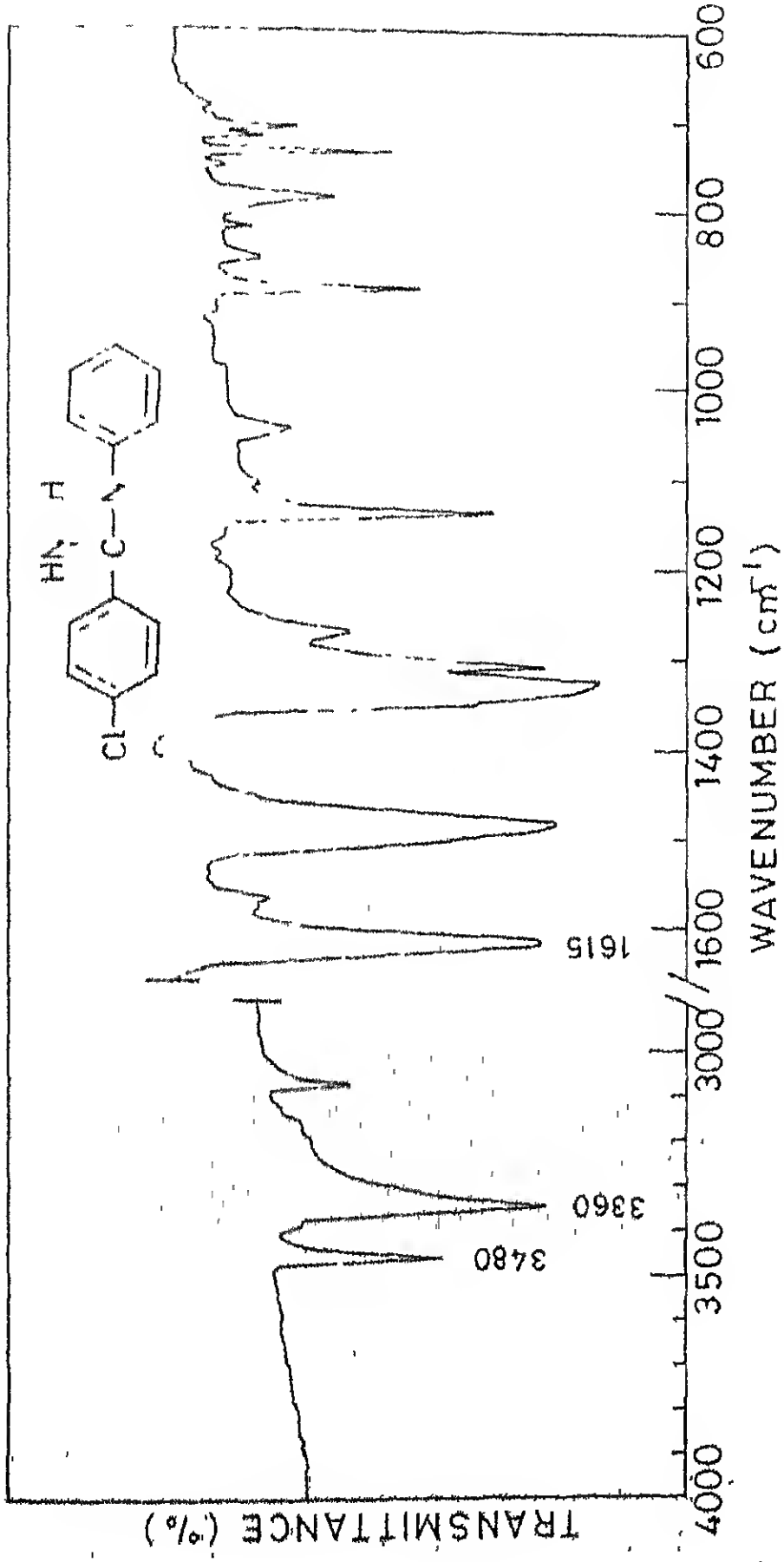


FIG. II.1 - IR SPECTRUM OF 85d.

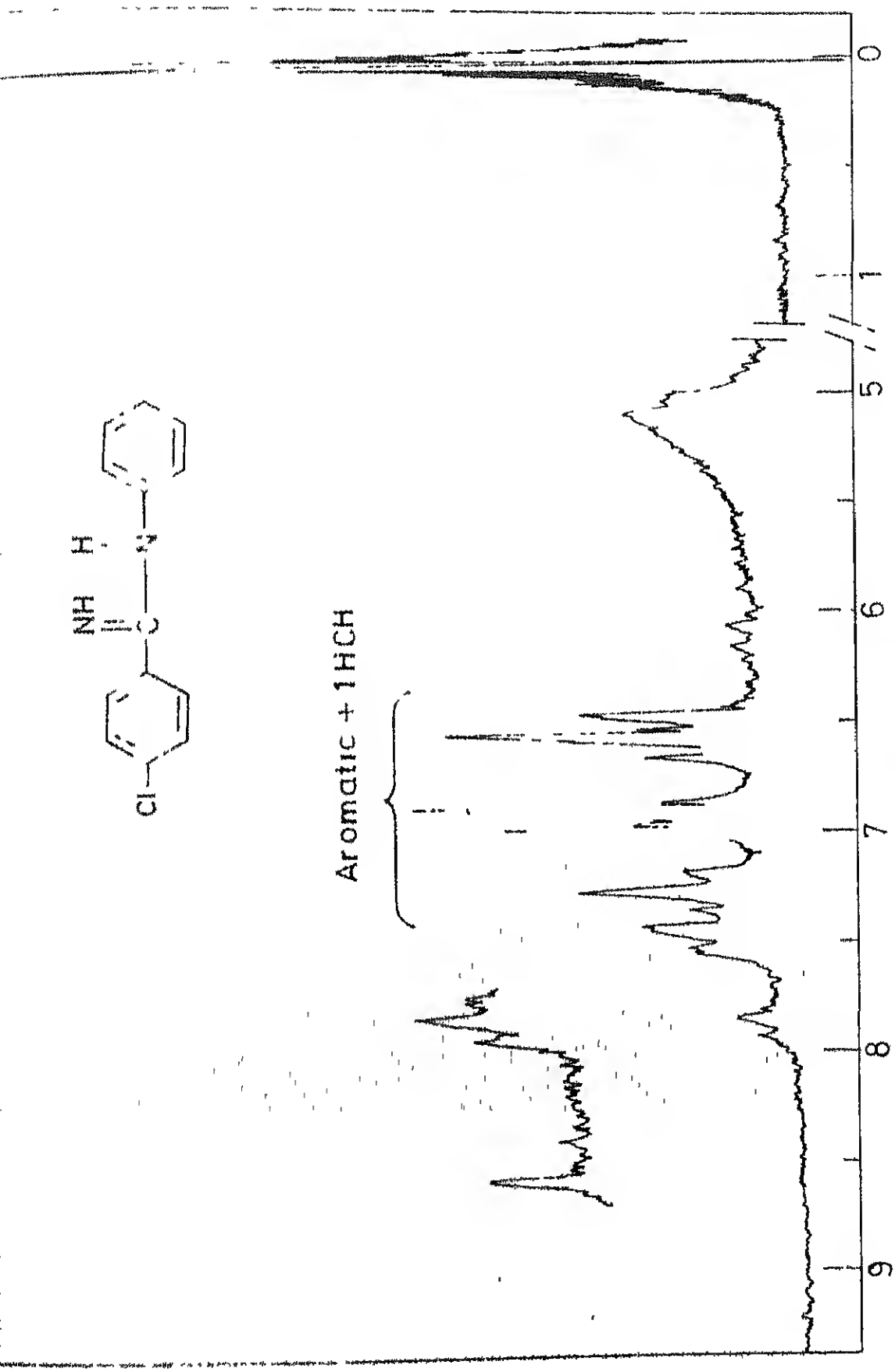
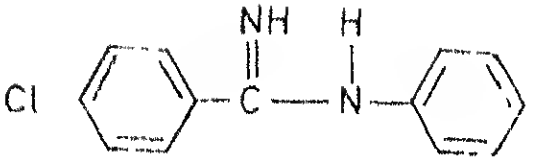


FIG. II.2 PMR SPECTRUM (90 MHz) OF 85d.



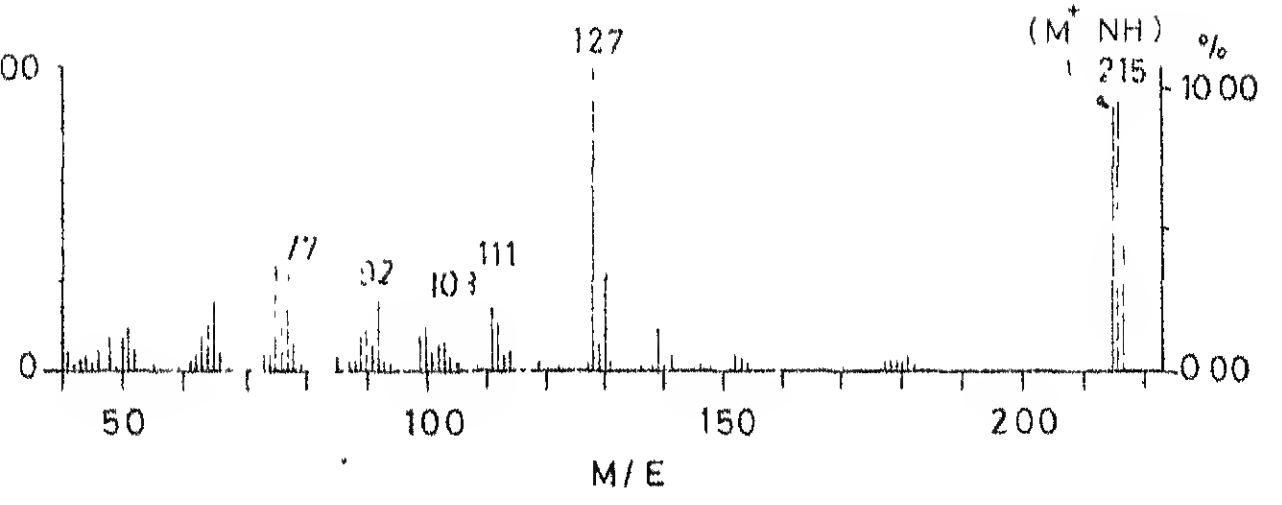


FIG. II.3 MASS SPECTRUM OF 85 d.

0, 1590($\nu_{C=N}$). It displayed PMR signals at δ5.2(s,1H,NH), hangeable with D_2O, 6.6-8.2(m, 9H, aromatic +1H,NH). It was ntified as 85f.

N-[p-nitro-benzylidene]-p-nitro-aniline on treatment with Cl_2-CH_3CN gave a compound which analysed for $C_{13}H_{10}N_4O_4$ l. formula). It gave molecular ion peak at 286, in the mass ctrum.

It displayed IR absorption bands at ν 3310, 3470(ν_{NH}), 1615 N), showing the presence of two NH groups. The compound ibited PMR signals at δ 5.2 (b, 1H, NH, exchangeable with D_2O), -8.1 (m, 8H, aromatic +1H,NH). It was identified as 85g.

N-[p-nitro-benzylidene]-m-nitro-aniline with sulphuryl oride in acetonitrile furnished a compound which on the basis elemental analysis corresponded to molecular formula $C_{13}H_{10}N_4O_4$. gave molecular ion peak at 286. It showed IR absorption ima at ν 3310, 3200(ν_{NH}), 1620($\nu_{C=N}$). It gave PMR signals at .3(s,1H,NH), 6.6-8.2(m,8H, aromatic + 1H,NH). It was identified 85h.

Treatment of N-[p-nitro-benzylidene]-o-nitro-aniline with phuryl chloride in acetonitrile gave rise to a compound which responded to molecular formula $C_{13}H_{10}N_4O_4$ on the basis of mental analysis. It gave molecular ion peak at 286, in the s spectrum. It gave IR absorption maxima at ν 3340, 3475(NH),

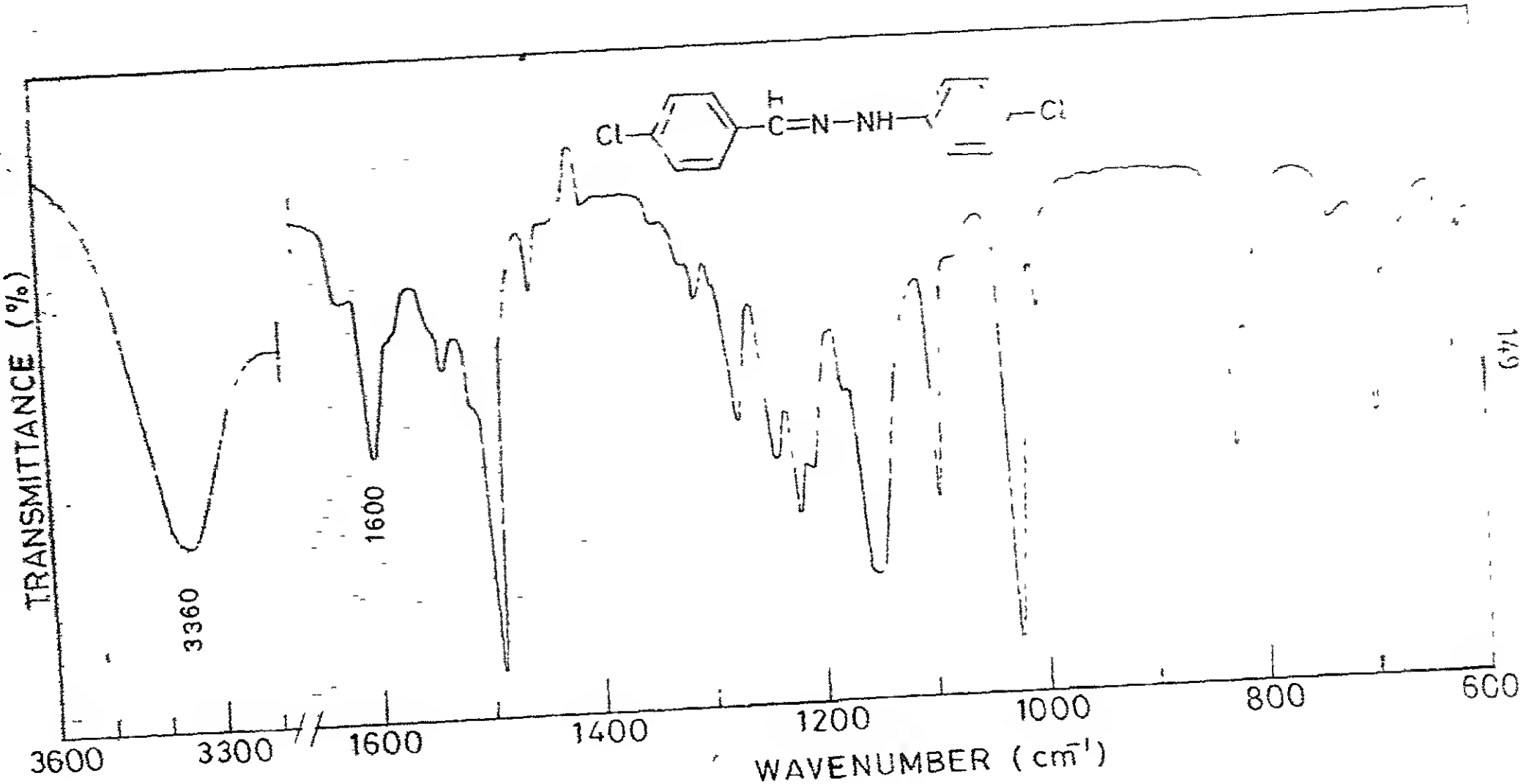


FIG. II.4 IR SPECTRUM OF 87b.

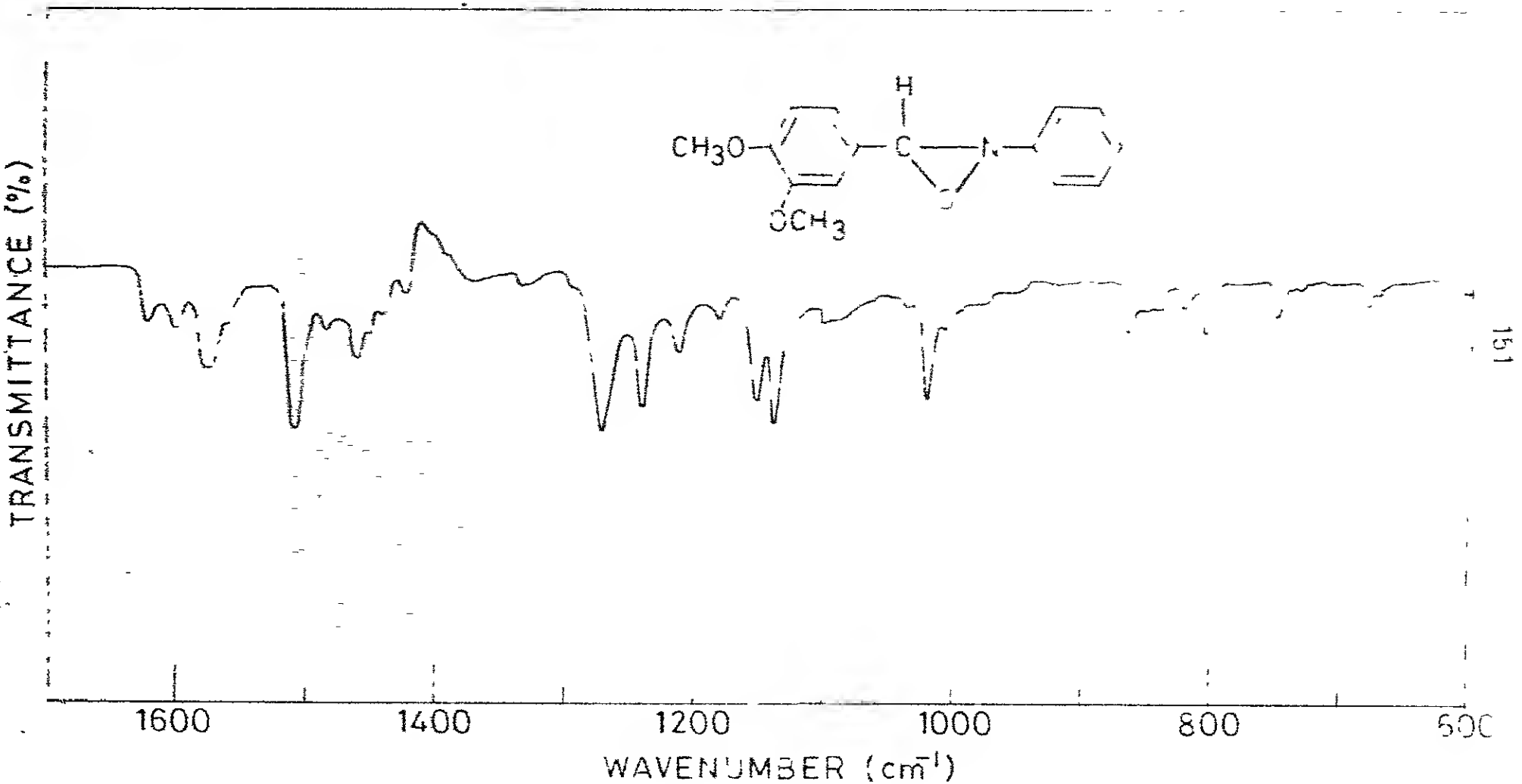


FIG. II.5 IR SPECTRUM OF 91n

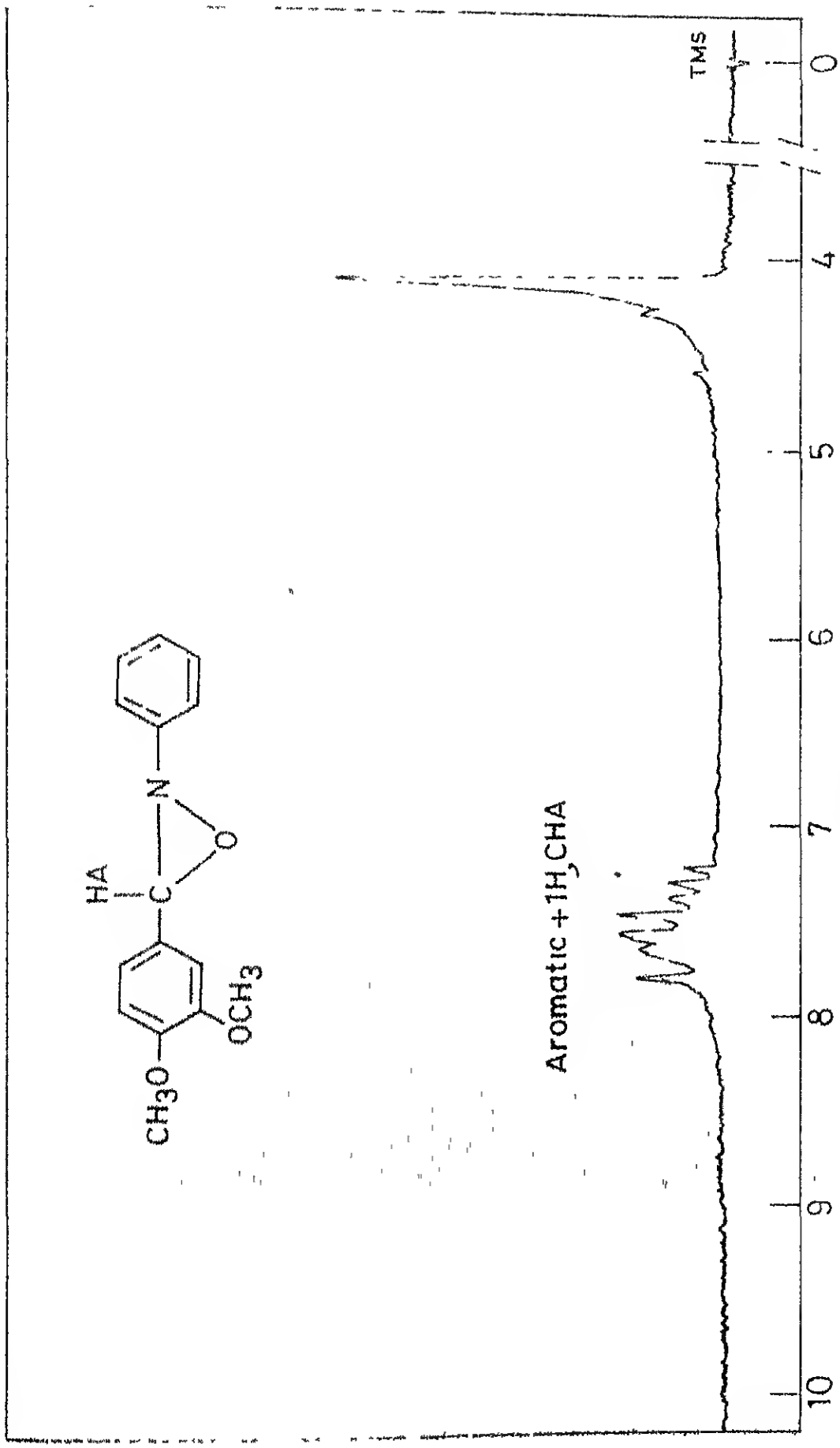


FIG. II.6 PMR SPECTRUM (90 MHz) OF 91 n.

SO_2Cl_2-CH_3CN reacts with N-[p-bromo-benzylidene]-p-nitro-aniline, resulting in the formation of 85m, which on the basis of elemental analysis corresponded to molecular formula $C_{15}H_{15}N_3O_4$. It gave molecular ion peak at 301 in the mass spectrum. It gave IR absorption bands at 3325, 3480(ν_{NH}), 1625($\nu_{C=N}$) cm^{-1}. It exhibited PMR signals at δ4.9(b,1H, NH, exchangeable with D_2O), 6.8-8.1 (m, 7H, aromatic + 1H, NH). It was identified as 85m.

On the basis of elemental analysis. 91n corresponded to the molecular formula $C_{14}H_{13}NO_2$. It gave molecular ion peak at 227 in the mass spectrum. IR spectrum revealed the absence of C=N bond (Fig.II.5). It gave PMR signals at δ7-7.9(m, 8H, aromatic + 1H, CH). It was identified as 91n (Fig.II.6).

On the basis of elemental analysis it corresponded to molecular formula $C_{15}H_5NO_3$. It gave a peak at m/e: 197($M^+-(OCH_3)_2$ in the mass spectrum. It exhibited IR absorption peak at 3260 (ν_{NH}), 1670($\nu_{C=O}$), 1595($\nu_{C=N}$) cm^{-1}. It gave PMR signals at δ3.9 (s, 6H, CH_3), 7.2-7.8 (m, 8H, aromatic + 1H, NH). It was identified as 95n.

On the basis of elemental analysis 95o corresponded to molecular formula $C_{15}H_{14}ClNO_3$. It gave molecular ion peak at 291 in the mass spectrum. It exhibited IR absorption bands at 3255(ν_{NH}), 1675($\nu_{C=O}$) cm^{-1}, (Fig.II.7), showing the presence of $-\overset{O}{\overset{\|}{C}}-NH$ group. It gave PMR signals at δ3.9(d, 6H, CH_3), 6.8-7.5 (m, 7H, aromatic + 1H, NH) (Fig.II.8). It was identified as 95o.

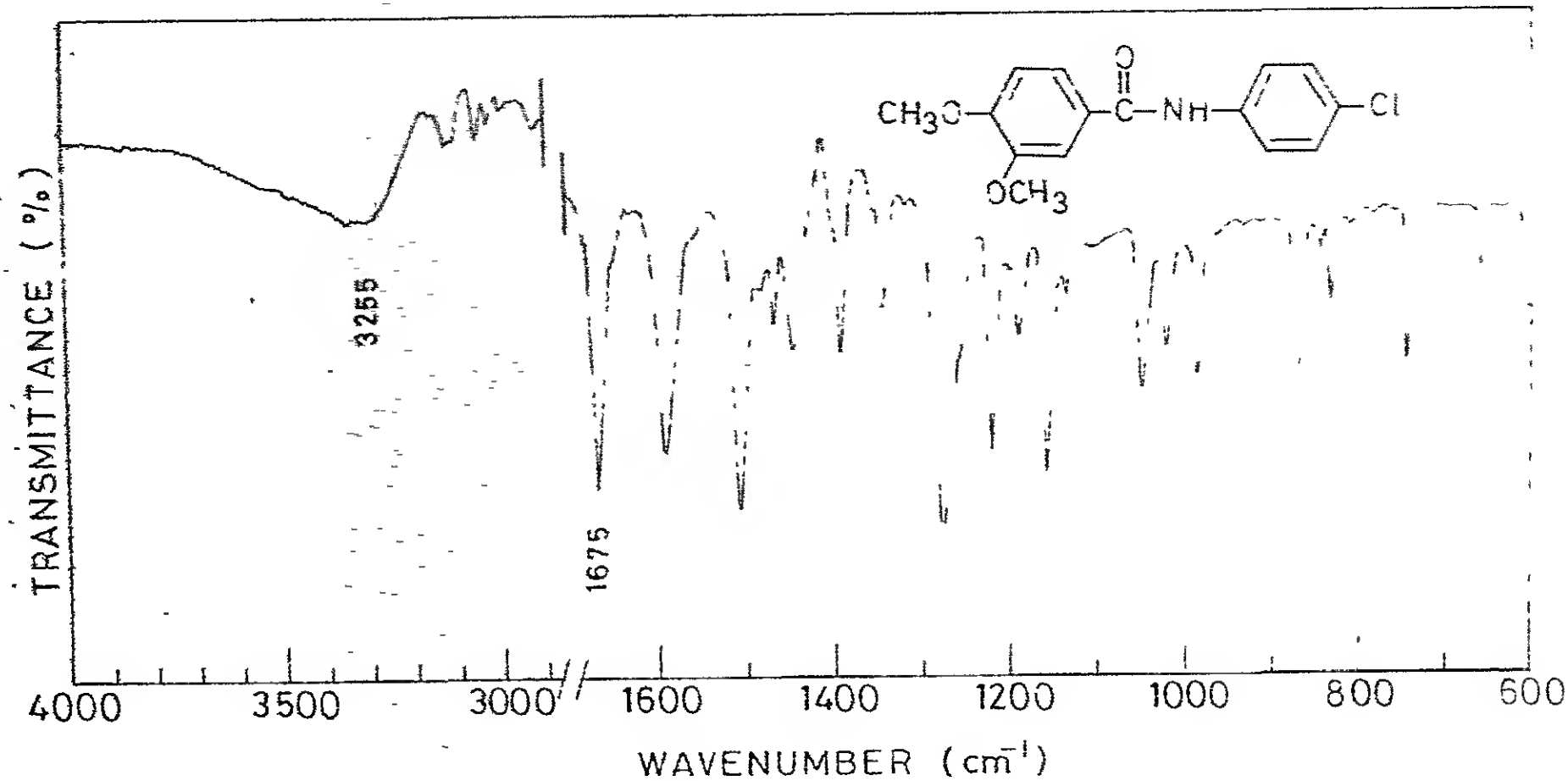


FIG. II.7 IR SPECTRUM OF 95 o.

On the basis of elemental analysis 95p corresponded to molecular formula $C_{14}H_{13}NO_2$. It gave molecular ion peak at 227 in the mass spectrum. It exhibited IR absorption maxima at 3250(ν_{NH}), 1670($\nu_{C=O}$), 1590($\nu_{C=N}$) cm^{-1}. It displayed PMR signals at δ 6-7.1 (m, 9H, aromatic + 1H, NH), 3.9(d, 3H, OCH_3). It was identified as 95p.

On the basis of elemental analysis 95q corresponded to molecular formula $C_{14}H_{12}ClNO_2$. It gave molecular ion peak at 261. It gave IR absorption maxima at 3250(ν_{NH}), 1670($\nu_{C=O}$), 1590, 1510($\nu_{C=N}$) cm^{-1}. It exhibited PMR signals at δ 3.9(d, 3H, OCH_3), 6.8-7.4(m, 9H, aromatic + 1H, NH), exchangeable with D_2O. It was identified as 95q.

On the basis of elemental analysis 95r corresponded to molecular formula $C_{16}H_{17}NO_4$. It gave molecular ion peak at 287. It exhibited IR absorptions at 3250(ν_{NH}), 1670($\nu_{C=O}$), 1590, 1510 cm^{-1}. It gave PMR signals at δ 6-7.1(m, 7H, aromatic + 1H, NH), exchangeable with D_2O. It was identified as 95r.

The elemental analysis of 98a indicates its molecular formula as $C_{14}H_{11}ClN_2$. It gave molecular ion peak at 242. The compound displayed IR absorption bands at 1610, 1580($\nu_{C=N}$) cm^{-1}. It exhibited PMR signals at δ 7.2-8.6(m, 10H, aromatic + 1H, CH, olefinic). The compound was identified as 98a.

On the basis of elemental analysis 98b corresponded to molecular formula $C_{18}H_{20}ClN_2O_4$. It gave molecular ion peak at 363

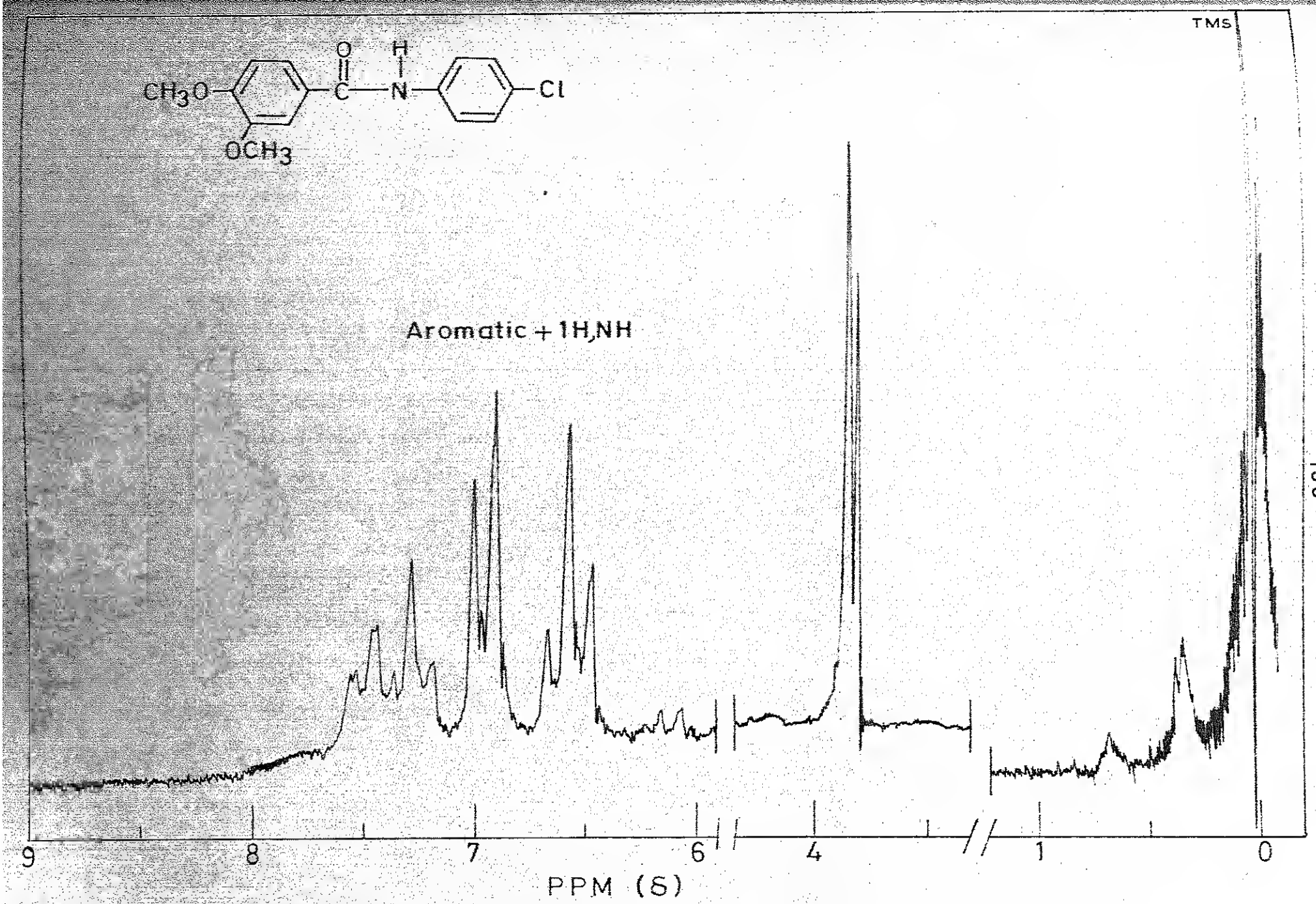
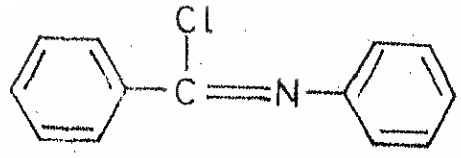


FIG. II.8 PMR SPECTRUM (90 MHz) OF 95 o.



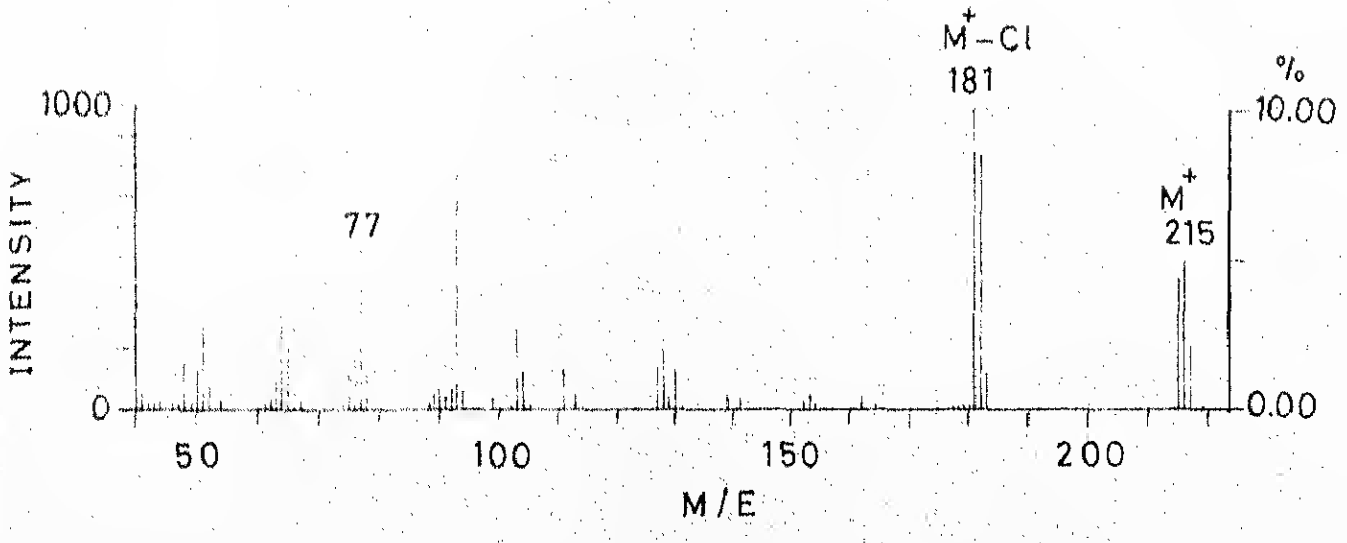


FIG. II. 9 MASS SPECTRUM OF 96e.

in the mass spectrum. It showed IR absorption bands at 1600, 1620($\nu_{C=N}$) cm^{-1}. It exhibited PMR signals at δ6.9-8.4(m, 6H, aromatic + 1H, CH, olefinic), 3.8(m, 12H, OCH_3). It was identified as 98b.

On the basis of elemental analysis 98c corresponded to molecular formula $C_{14}H_9Cl_3N_2$. It gave molecular ion peak at 310 in the mass spectrum. It gave IR absorption maxima at 1600, 1595 ($\nu_{C=N}$) cm^{-1}. It displayed PMR signals at δ7.5-8.2(m, 8H, aromatic + 1H, CH, olefinic). It was identified as 98c.

On the basis of elemental analysis 98d corresponded to molecular formula $C_{14}H_9ClN_4O_4$. It gave molecular ion peak at 332, in the mass spectrum. It gave IR absorption maxima at 1595, 1610 ($\nu_{C=N}$) cm^{-1}. It gave PMR signals at δ6.9-8.4(m, 8H, aromatic + 1H, CH, olefinic). It was identified as 98d.

On the basis of elemental analysis 98e corresponded to molecular formula $C_{14}H_9ClBr_2N_2$. It gave molecular ion peak at 400, in the mass spectrum (Fig.II.12). It exhibited IR absorption maxima at 1605, 1590($\nu_{C=N}$) cm^{-1} (Fig.II.10). It gave PMR signals at δ 7.4-8.25(m, 8H, aromatic + 1H, CH, olefinic) (Fig.II.11). It was identified as 98e.

On the basis of elemental analysis 98f corresponded to molecular formula $C_{16}H_{15}ClN_2O_2$. It gave molecular ion peak at 302. It exhibited IR absorption maxima at 1595, 1610($\nu_{C=N}$) cm^{-1}. It gave PMR signals at δ 6.9-8.4(m, 8H, aromatic + 1H, CH, olefinic), 3.8 (m, 6H, OCH_3). It was identified as 98f.

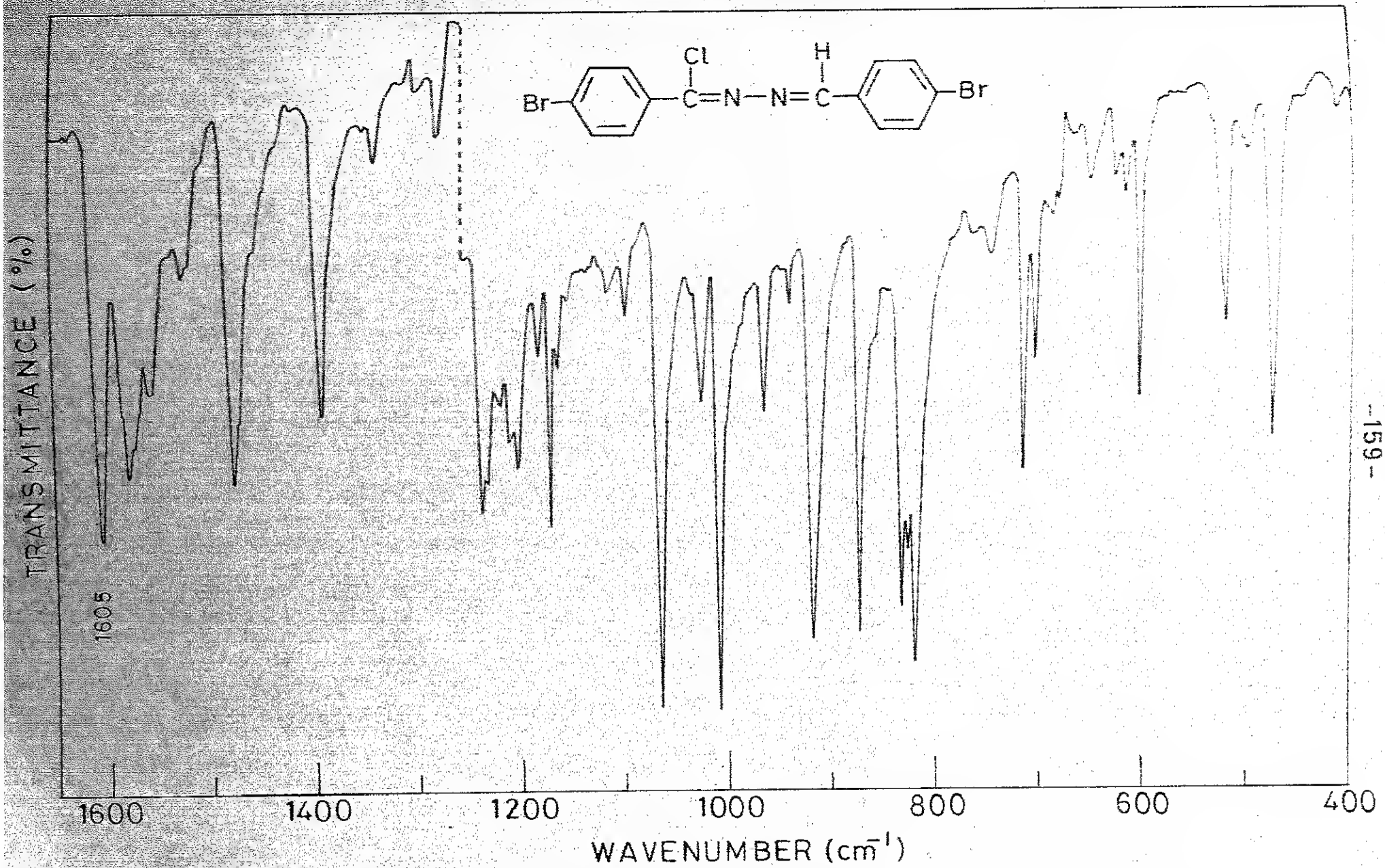


FIG. II.10 IR SPECTRUM OF 98 e.

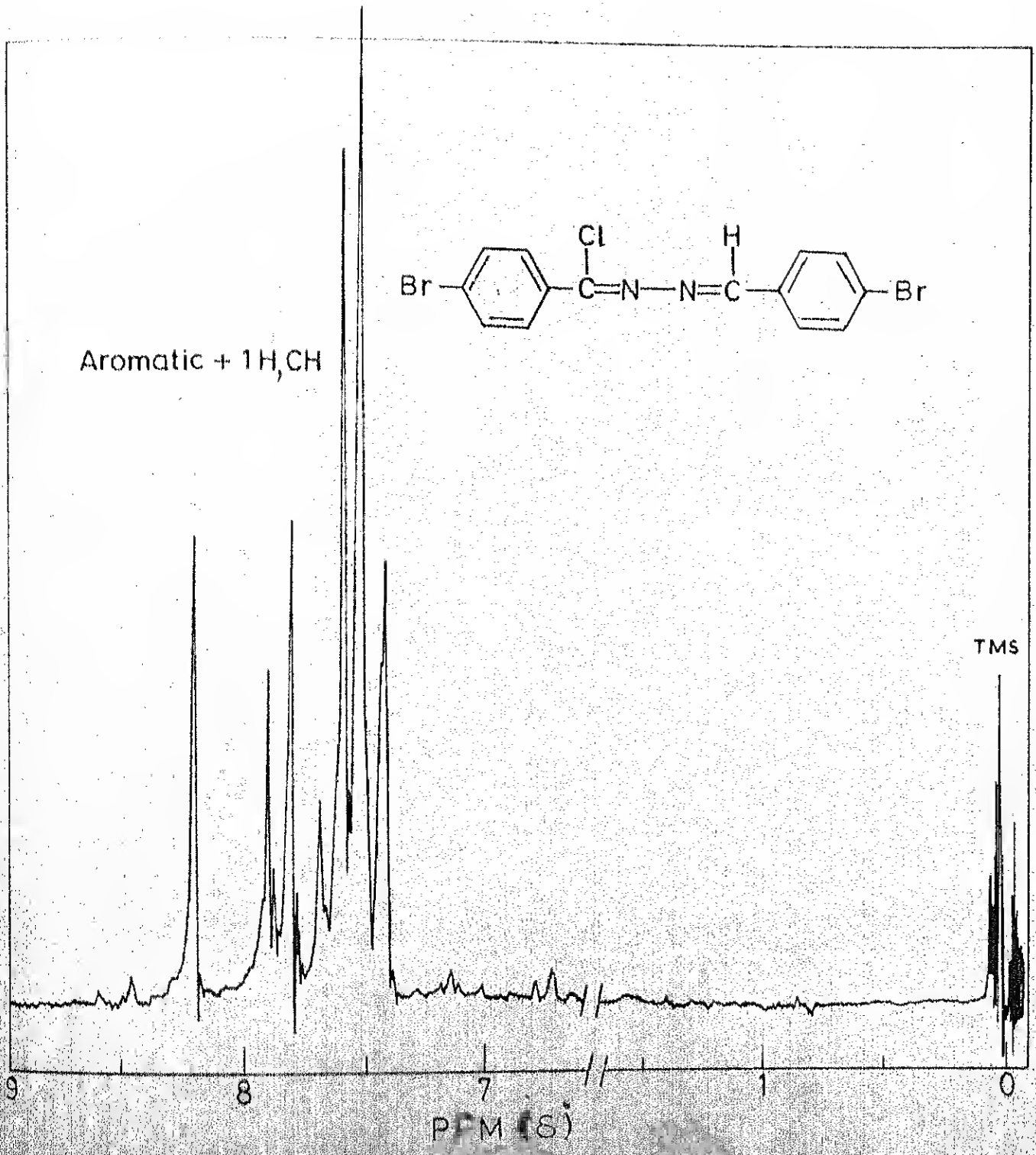
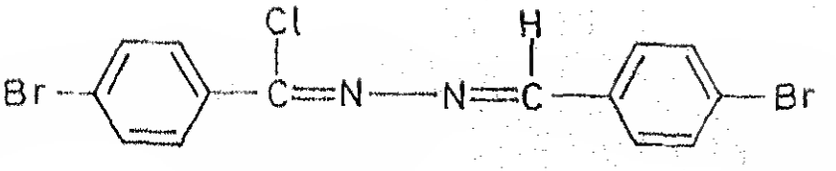


FIG. II.11 PMR SPECTRUM (90 MHz) OF 98 e.



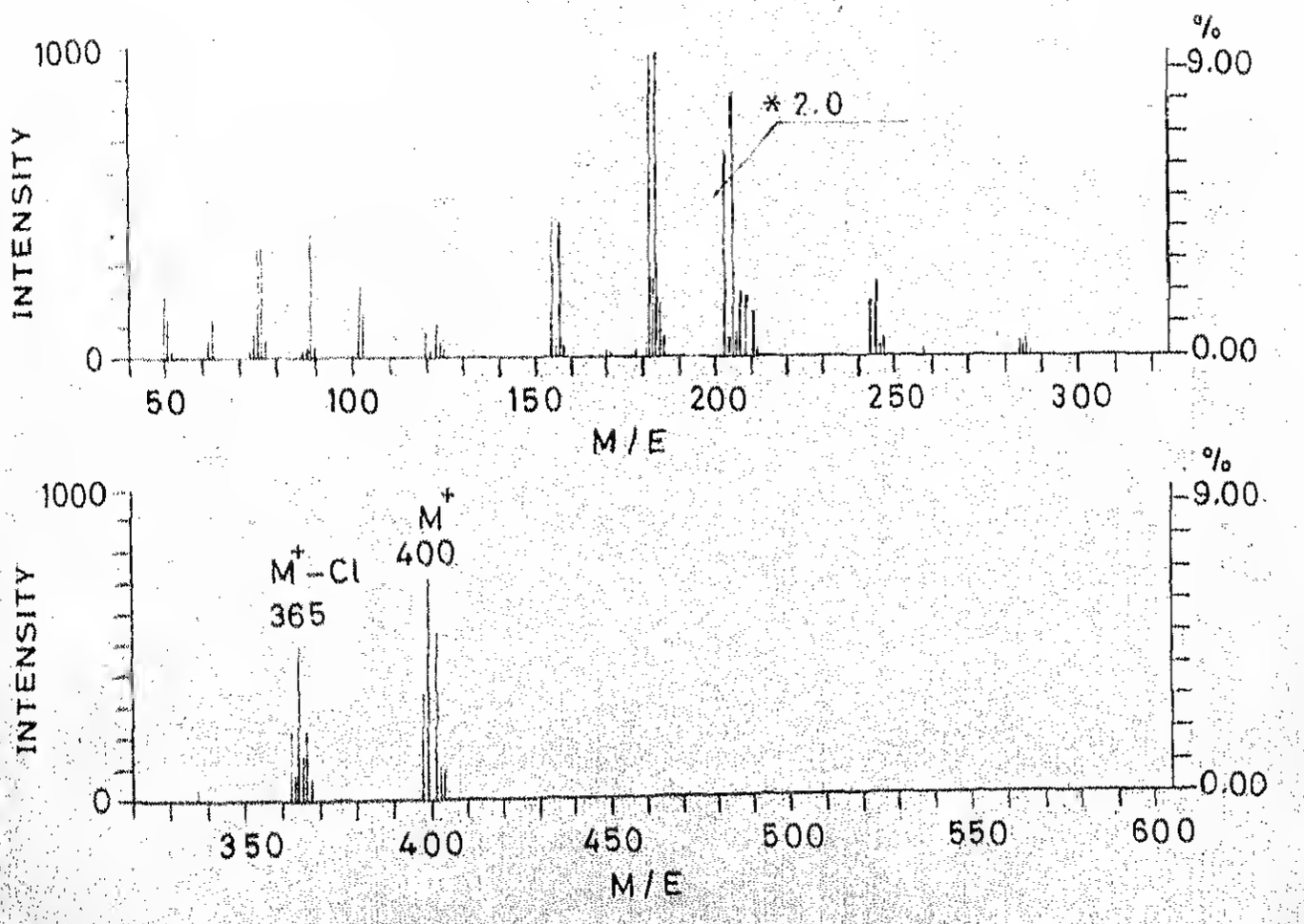


FIG. II.12 MASS SPECTRUM OF 98e.

EXPERIMENTAL

All the melting points are uncorrected and were taken on a Fisher-Johns melting point apparatus. The IR spectra were recorded on Perkin-Elmer model-580 infrared spectrophotometers. Proton magnetic resonance (PMR) spectra were recorded on Varian EM-390 (90 MHz) instrument. Chemical shifts are reported in parts per million down field from the internal reference TMS(δ). Multiplicity is indicated using the following abbreviations: s(singlet), bs(broad singlet), d(doublet), t(triplet), q(quartet) and m(multiplet). Mass spectra were recorded on a Jeol-300D mass spectrometer at 70 eV.

Starting materials

Freshly distilled sulphuryl chloride (Riedal) and dry acetonitrile, benzonitrile, dimethyl sulphoxide, ethyl cyano-acetate and dichloromethane were used. All the Schiff's bases used in the experiments were prepared according to the methods described elsewhere (vide-infra).

N-[benylidene]-aniline, N-[p-bromobenzylidene]-aniline, N-[p-chloro-benzylidene]-p-chloro-aniline, N-[p-chloro-benzylidene]-aniline, N-[benzylidene]-p-chloro-aniline, N-[p-bromo-benzylidene]-p-chloro-aniline, N-[benzylidene]-p-nitro-aniline, N-[p-nitro-benzylidene]-p-nitro-aniline, N-[p-nitro-benzylidene]-m-nitro-aniline, N-[p-nitro-benzylidene]-o-nitro-aniline,

N-[benzylidene]-o-nitro-aniline, N-[benzylidene]-m-nitro-aniline, N-[p-bromo-benzylidene]-p-nitro-aniline, N-[3,4-dimethoxy-benzylidene]-m-nitro-aniline, N-[p-methoxy-benzylidene]aniline, N-[p-methoxy-benzylidene]-p-chloro-aniline, N-[3,4-dimethoxy-benzylidene]-aniline, N-[3,4-dimethoxy-benzylidene]-p-methoxy-aniline, N-[3,4-dimethoxy-benzylidene]-p-chloro-aniline.

Preparation of Benzamidines(94d-m)

General procedure: Sulphuryl chloride (0.18 ml, 0.005 mol) in dry $CH_3CN/C_6H_5CN/CNCH_2CO_2Et-CH_2Cl_2$ (5 ml) was added dropwise over a period of 5 minutes to a magnetically stirred solution of Schiff's base 78d (0.005 mol) in $CH_3CN/C_6H_5CN/CNCH_2CO_2Et-CH_2Cl_2$ (10 ml) at 0°. After the expiry of ten minutes, the mixture was diluted with water, stirred at room temperature for additional twenty minutes and extracted with dichloromethane (3x2 ml). The organic layer was washed with water, dried (Na_2SO_4) and the solvent was evaporated off. The residue obtained was purified by crystallization from ethanol and furnished 94d.

Note: The modified Ritter reaction can be used to prepare a variety of compounds (noted below) by employing the following reactants (shown in parenthesis). Thus benzanilides, 95n-r ($DMSO-CH_2Cl_2$), α-chloro-aldazine, 98a-f (CH_3CN), oxaziridine, 91n ($DMSO-CH_2Cl_2$), N-phenyl-benzamid-chloride, 96e, ($CNCH_2CO_2Et-CH_2Cl_2$),

and benzaldehyde-phenyl-hydrazone, 87a-c (CH_3CN/C_6H_5CN) are preparable by the above method.

Synthesis of 87a:

Yield (.976g), 71%, m.p. 169-170°, (lit.170°).

Anal for $C_{13}H_{11}BrN_2$: Calcd, C, 56.72; H, 4.00; N, 10.18%
Found, C, 56.69; H, 3.98; N, 10.00%

IR Spectrum (KBr), ν_{max}: 3300(ν_{NH}), 1600($\nu_{C=N}$), 1200,1040,740,620.

PMR Spectrum ($DMSOd_6$):δ4.9(s, 1H, NH), 6.4-7.4(m, 9H, aromatic +1H,CH, olefinic).

Mass spectrum, m/e: 275(M^+), 260, 184, 183, 156, 92, 77.

Synthesis of 87b:

Yield:0.854g, (65%),m.p. 112-113°.

Anal for $C_{13}H_9Cl_2N_2$: Calcd, C, 59.32; H, 3.42; N, 10.65%
Found, C, 59.30; H, 3.40; N, 10.59%

IR Spectrum (KBr), ν_{max}: 3350(ν_{NH}), 1595($\nu_{C=N}$), 1195, 1030, 740, 620 (cm^{-1}).

PMR Spectrum($DMSOd_6$):δ5.0(s, 1H, NH), 6.5-7.4(m, 8H, aromatic + 1H,CH,olefinic).

Mass spectrum, m/e: 263(M^+), 250, 126, 112.

Synthesis 87c:

Yield: 0.695g, (71%), m.p. 157-158°, (lit.160°).

Anal for $C_{13}H_{12}N_2$: Calcd, C, 79.59; H, 6.12; N, 14.28%
Found, C, 80.51; H, 7.76; N, 13.42%

IR Spectrum(KBr), ν_{max}: 3360(ν_{NH}), 1590($\nu_{C=N}$), 1190,1030,740,620 cm^{-1}.

PMR Spectrum ($DMSOd_6$), δ ppm: 6.4-7.0(m, 10H, aromatic + 1H, CH, olefinic).

Mass spectrum, m/e: 196(M^+), 139, 92.

Synthesis of 85d:

Yield: 0.741g, (65%), m.p. 115-116°.

Anal for $C_{13}H_{11}ClN_2$: Calcd, C, 67.82; H, 4.78; N, 12.17%
Found, C, 68.76; H, 3.61; N, 13.56%

IR Spectrum(KBr), ν_{max}: 3360, 3480(ν_{NH}), 1615, 1590($\nu_{C=N}$), 1470, 1320, 1110, 840, 750 cm^{-1}.

PMR Spectrum($DMSOd_6$), δ ppm: 5.0(s, 1H, NH), 6.5-7.7(m, 9H, aromatic + 1H, NH), exchangeable with D_2O.

Mass spectrum, m/e: 215(M^+-NH), 127, 111, 92, 77.

Synthesis of 96e:

Yield: 0.813g, (65%), m.p. 219-220°.

Alal for $C_{13}H_9Cl_2N$: Calcd, C, 62.15; H, 3.60; N, 5.60%
Found, C, 61.56; H, 4.42; N, 6.21%

IR Spectrum(KBr), ν_{max}: 1600($\nu_{C=N}$), 1460, 1260, 1010, 820, 690, 620.

PMR Spectrum($DMSOd_6$), δppm: 5.8-7.1(m, 9H, aromatic).

Mass spectrum, m/e: 215(M^+-Cl), 112, 77.

Synthesis of 85f:

Yield:0.783g, (65%), m.p. 172-173°.

Anal for $C_{13}H_{11}N_3O_2$: Calcd, C, 64.73; H, 4.56; N, 17.42%
Found, C, 64.69; H, 4.48; N, 17.37%

IR Spectrum(KBr), ν_{max}: 3320, 3460(ν_{NH}), 1620, 1590($\nu_{C=N}$), 1470, 1300, 1110, 840, 750 cm^{-1}.

PMR Spectrum($CDCl_3$), δppm: 5.2(s, 1H, NH), exchangeable with D_2O, 6.6-8.2(m, 8H, aromatic +1H, NH).

Mass spectrum, m/e: 241(M^+), 138, 123, 77.

Synthesis of 85g:

Yield:0.972g, (68%), m.p. 194-195°.

Anal for $C_{13}H_{10}N_4O_4$: Calcd, C, 54.54; H, 3.49; N, 19.58%
Found, C, 54.47; H, 3.39; N, 19.42%

IR Spectrum(KBr), ν_{max}: 3310, 3470(ν_{NH}), 3085, 1615($\nu_{C=N}$), 1480, 1330, 1140, 890, 730. cm^{-1}.

PMR Spectrum($CDCl_3$), δ ppm: 5.2(b, 1H, NH, exchangeable with D_2O), 6.5-8.1(m, 8H, aromatic + 1H, NH).

Mass spectrum, m/e: 286(M^+), 164, 137, 123, 77.

Synthesis of 85h:

Yield: 0.915g, (64%), m.p. 196-197°.

Anal for $C_{13}H_{10}N_4O_4$: Calcd, C, 54.54; H, 3.49; N, 19.58%
Found, C, 55.65; H, 4.12; N, 20.02%

IR Spectrum(KBr), ν_{max}: 3310, 3200(ν_{NH}), 1620($\nu_{C=N}$) cm^{-1}.

PMR Spectrum($CDCl_3$), δ ppm: 5.3(s, 1H, NH, exchangeable with D_2O), 6.6-8.2(m, 8H, aromatic + 1H, NH).

Mass spectrum, m/e: 286(M^+), 137, 123, 77.

Synthesis of 85i:

Yield: 0.900g, (62%), m.p. 105-106°.

Anal for $C_{13}H_{10}N_4O_4$: Calcd, C, 54.54; H, 3.49; N, 19.58%
Found, C, 53.68; H, 4.64; N, 20.51%

IR Spectrum(KBr), ν_{max}: 3340, 3475(ν_{NH}), 1615($\nu_{C=N}$), 1200, 875, 830 cm^{-1}.

PMR Spectrum(Aceton d_6), δ ppm: 5.1(s, 1H, NH, exchangeable with D_2O), 6.3-8.0(m, 8H, aromatic + 1H, NH).

Mass spectrum, m/e: 286(M^+), 164, 137, 123, 77.

Synthesis of 85j:

Yield:0.807g, (67%), m.p. 88-89°.

Anal for $C_{13}H_{11}N_3O_2$: Calcd, C, 64.73; H, 4.56; N, 17.42%
Found, C, 63.68; H, 5.21; N, 18.56%

IR Spectrum(KBr), ν_{max}: 3340, 3480(ν_{NH}), 1610($\nu_{C=N}$), 1480, 1320, 1140, 890, 740 cm^{-1}.

PMR Spectrum(acetone d_6), δ ppm: 5.0(s,1H, NH, exchangeable with D_2O), 6.1-8.4(m, 9H, aromatic + 1H, NH).

Mass spectrum, m/e: 241(M^+), 123, 119, 77.

Synthesis of 85k:

Yield:0.831g, (69%),m.p. 95-96°.

Anal for $C_{13}H_{11}N_3O_2$: Calcd, C, 64.73; H, 4.56; N, 17.42%
Found, C, 64.68; H, 4.50; N, 17.40%

IR Spectrum(KBr), ν_{max}: 3340(ν_{NH}), 3480, 1620($\nu_{C=N}$), 1205, 880, 830 cm^{-1}.

PMR Spectrum($CDCl_3$), ppm: 5.1(s, 1H, NH), exchangeable with D_2O, 6.2-8.5(m, 9H, aromatic +1H,NH).

Mass spectrum, m/e: 241(M^+), 123, 119, 77.

Synthesis of 85l:

Yield:0.960g, (60%),m.p. 155-156°.

Anal for $C_{13}H_{10}BrN_3O_2$: Calcd, C, 48.75; H, 3.12; N, 13.12%
Found, C, 48.69; H, 3.01; N, 13.10%

IR Spectrum(KBr), ν_{max}: 3325, 3480(ν_{NH}), 1625($\nu_{C=N}$), 1480, 1330 cm^{-1}.

PMR Spectrum($CDCl_3$), δ ppm: 4.9(d, 1H, NH, exchangeable with D_2O), 6.6–8.2(m, 8H, aromatic +1H, NH).

Mass spectrum, m/e: 320(M^+), 240(M^+-Br), 198, 137, 123, 77.

Synthesis of 85m:

Yield: 0.977g, (65%), m.p. 175–176°.

Anal for $C_{15}H_{15}N_3O_4$: Calcd, C, 59.80; H, 4.98; N, 13.95%
Found, C, 59.75; H, 4.96; N, 13.90%

IR Spectrum(KBr), ν_{max}: 3325, 3480(ν_{NH}), 1625($\nu_{C=N}$), 1480, 1330, 1305, 1110, 895, 840 cm^{-1}.

PMR Spectrum(acetone d_6), δ ppm: 4.9(b, 1H, NH, exchangeable with D_2O), 6.8–8.1(m, 7H, aromatic, + 1H, NH), 3.8(s, 6H, OCH_3).

Mass spectrum, m/e: 301(M^+), 179, 137, 123, 77.

Synthesis of 95n:

Yield: 0.829g 64% m.p. 141–142°.

Anal for $C_{15}H_{15}O_3N$: Calcd, C, 69.50; H, 5.80; N, 5.40%
Found, C, 70.00; H, 5.78; N, 5.39%

IR Spectrum(KBr), ν_{max}: 3260(ν_{NH}), 1670($\nu_{C=O}$), 1595, 1510, 1275, 1220, 1050, 870, 610 cm^{-1}.

PMR Spectrum(DMSO d_6), δ ppm: 3.9(s,6H, OCH_3), 7.2-7.8(m, 8H, aromatic +1H, NH).

Mass spectrum, m/e: 197(M^+-$(OCH_3)_2$, 138, 107, 92, 77.

Synthesis of 91n:

Yield:0.795g , (70%), m.p. 81-82°.

Anal for $C_{14}H_{13}NO_2$: Calcd, C, 74.00; H, 5.72; N, 6.16%
Found, C, 73.98; H, 5.69; N, 6.15%

IR Spectrum(KBr), ν_{max}: 1500, 1270 cm^{-1}.

PMR Spectrum(DMSO d_6), δ ppm:7.2-7.9 (m, 8H, aromatic +1H, CH, olefinic).

Mass spectrum, m/e: 227(M^+), 165, 93, 77.

Synthesis of 95o:

Yield: 0.946, (65%), m.p. 124-125°.

Anal for $C_{15}H_{14}ClNO_3$: Calcd, C, 61.85; H, 4.81; N, 4.81%
Found, C, 61.75; H, 4.78; N, 4.80%

IR Spectrum(KBr), ν_{max}: 3255(ν_{NH}), 1675($\nu_{C=O}$), 1595, 1510, 1270, 870, 740 cm^{-1}.

PMR Spectrum($CDCl_3$), δ ppm: 3.9(d,6H,OCH_3), 6.8-7.5(m, 7H, aromatic +1H, NH).

Mass spectrum,m/e: 291(M^+), 137, 112, 92, 77.

Synthesis of 95p:

Yield:0.726g, (64%), m.p. 148-149°.

Anal for $C_{14}H_{13}NO_2$: Calcd, C, 74.00; H, 5.72; N, 6.16%
Found, C, 73.98; H, 5.61; N, 6.18%

IR Spectrum(KBr), ν_{max}: 3250(ν_{NH}), 1670($\nu_{C=O}$), 1590, 1510, 1270, 875, 740 cm^{-1}.

PMR Spectrum(DMSO d_6), δ ppm: 4.0(m, 9H, OCH_3), 6-7.1(m, 9H, aromatic +1H, NH).

Mass spectrum, m/e: 227(M^+).

Synthesis of 95q:

Yield:0.848g, (65%), m.p. 155-156°.

Anal for $C_{14}H_{12}ClNO_2$: Calcd, C, 64.36; H, 4.60; N, 5.36%
Found, C, 64.29; H, 4.57; N, 5.30%

IR Spectrum(KBr), ν_{max}: 3250(ν_{NH}), 1670($\nu_{C=O}$), 1590, 1510, 1270, 875, 740 cm^{-1}.

PMR Spectrum(acetone d_6), δ ppm: 3.9(d, 3H, OCH_3), 6.8-7.4(m, 8H, aromatic +1H, NH).

Mass spectrum, m/e: 261(M^+), 230, 150, 127, 112, 77.

Synthesis of 95r:

Yield:0.904g, (63%), m.p. 112-113°.

Anal for $C_{16}H_{17}NO_4$: Calcd, C, 66.89; H, 5.92; N, 4.87%

Found, C, 66.71; H, 5.64; N, 4.80%

IR Spectrum(KBr), ν_{max}: 3250(ν_{NH}), 1670($\nu_{C=O}$), 1590, 1510, 1270, 870, 735 cm^{-1}.

PMR Spectrum(DMSO d_6), δ ppm: 3.9–4.1 (m, 9H, OCH_3), 6–7.1(m, 7H, aromatic 1H, NH).

Mass spectrum, m/e: 287(M^+), 138, 122, 77.

Synthesis of 98a:

Yield: 0.847g, (70%), m.p. 110–111°.

Anal for $C_{14}H_{11}ClN_2$: Calcd, C, 69.42; H, 4.54; N, 11.57%

Found, C, 69.40; H, 5.35; N, 11.48%

IR Spectrum(KBr), ν_{max}: 1610, 1580($\nu_{C=N}$), 1450, 1205, 910, 760, 690, 600 cm^{-1}.

PMR Spectrum(acetone d_6), δ ppm: 7.2–8.6(m, 10H, aromatic + 1H, CH).

Mass spectrum, m/e: 242(M^+), 173.

Synthesis of 98b:

Yield: 1.36g, (75%), m.p. 189–190°.

Anal for $C_{18}H_{20}ClN_2O_4$: Calcd, C, 59.50; H, 5.50; N, 7.71%

Found, C, 59.49; H, 5.47; N, 7.60%

IR Spectrum(KBr), ν_{max}: 1600, 1620($\nu_{C=N}$), 1450, 1200, 910, 760, 690.

Synthesis of 98e:

Yield: 1.42g, (71%), m.p. 160-161°.

Anal for $C_{14}H_9ClBr_2N_2$: Calcd, C, 42.00; H, 2.25; N, 7.00%
Found, C, 42.96; H, 3.89; N, 8.02%

IR Spectrum(KBr), ν_{max}: 1605, 1590($\nu_{C=N}$), 1455, 1205, 760, 695 cm^{-1}.

PMR Spectrum($DMSOd_6$), δ ppm: 7.4-8.25(m, 8H, aromatic + 1H, CH, olefinic).

Mass spectrum, m/e: 400(M^+), 365(M^+-Cl).

Synthesis of 98f:

Yield: 1.06g, (70%), m.p. 150-151°.

Anal for $C_{16}H_{15}ClN_2O_2$: Calcd, C, 63.57; H, 4.96; N, 9.27%
Found, C, 64.65; H, 5.64; N, 10.10%

IR Spectrum(KBr), ν_{max}: 1595, 1610($\nu_{C=N}$), 1200, 915, 760, 690 cm^{-1}.

PMR Spectrum($DMSOd_6$), δ ppm: 6.9-8.4(m, 8H, aromatic + 1H, CH, olefinic), 3.8(m, 6H, OCH_3).

Mass spectrum, m/e: 302(M^+), 267(M^+-Cl).

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CHAPTER-III

CERIC AMMONIUM NITRATE OXIDATION OF SOME ESTERS, ALDAZINES & HETEROCYCLES

III.1 ABSTRACT

Ceric ammonium nitrate oxidation of some esters, aldazines and heterocycles have been investigated. The esters, aldazines and heterocycles taken for the present study include , Methyl-benzoate, ethyl-benzoate, n-propyl-benzoate, ethyl-p-chloro-benzoate, ethyl-m-chlorobenzoate, ethyl-p-nitro-benzoate, ethyl-p-bromo-benzoate, allyl-benzoate, allyl-m-chloro-benzoate, allyl-p-chloro-benzoate, allyl-p-nitro-benzoate, allyl-p-toluate, allyl-p-methoxy-benzoate, benzyl-benzoate, benzyl-p-chloro-benzoate, benzyl-p-toluate, ethyl-phenyl-acetate, n-propyl-phenyl-acetate. Aldazines (139a-j) (substiuents are given in Table III.2), 1-phenyl-3-methyl-2-pyrazolin-5-one, 1-[4-dinitro-phenyl]-3-methyl-2-pyrazolin-5-one, 1,2,3,4-tetrahydro-carbazole, and 1-[2,4-dinitro-phenyl]-3,5-dimethyl-pyrazole.

Oxidative cleavage of esters with CAN gave rise to their corresponding acids. While aldazines (139a-j) on similar treatment produced their corresponding aldehydes, characterized as 2,4-dinitro-phenyl-hydrazones).

Reaction of CAN with 1-phenyl-3-methyl-2-pyrazolin-5-one, 1-[4-nitro phenyl]-3-methyl-2-pyrazolin-5-one, 1,2,3,4-tetrahydrocarbazole, gave rise to 4-4'-bis-1-phenyl-3-methyl-2-pyrazolin-5-one, 4-4'-bis-1-[4-nitro-phenyl]-3-methyl-2-pyrazolin-5-one, N-N'-bis-1,2,3,4-tetrahydro-carbazole respectively.

The treatment of 1-[2,4-dinitro-phenyl]-3,5-dimethyl-pyrazole produced a hitherto unreported heterocycle (148d).

III.2 INTRODUCTION

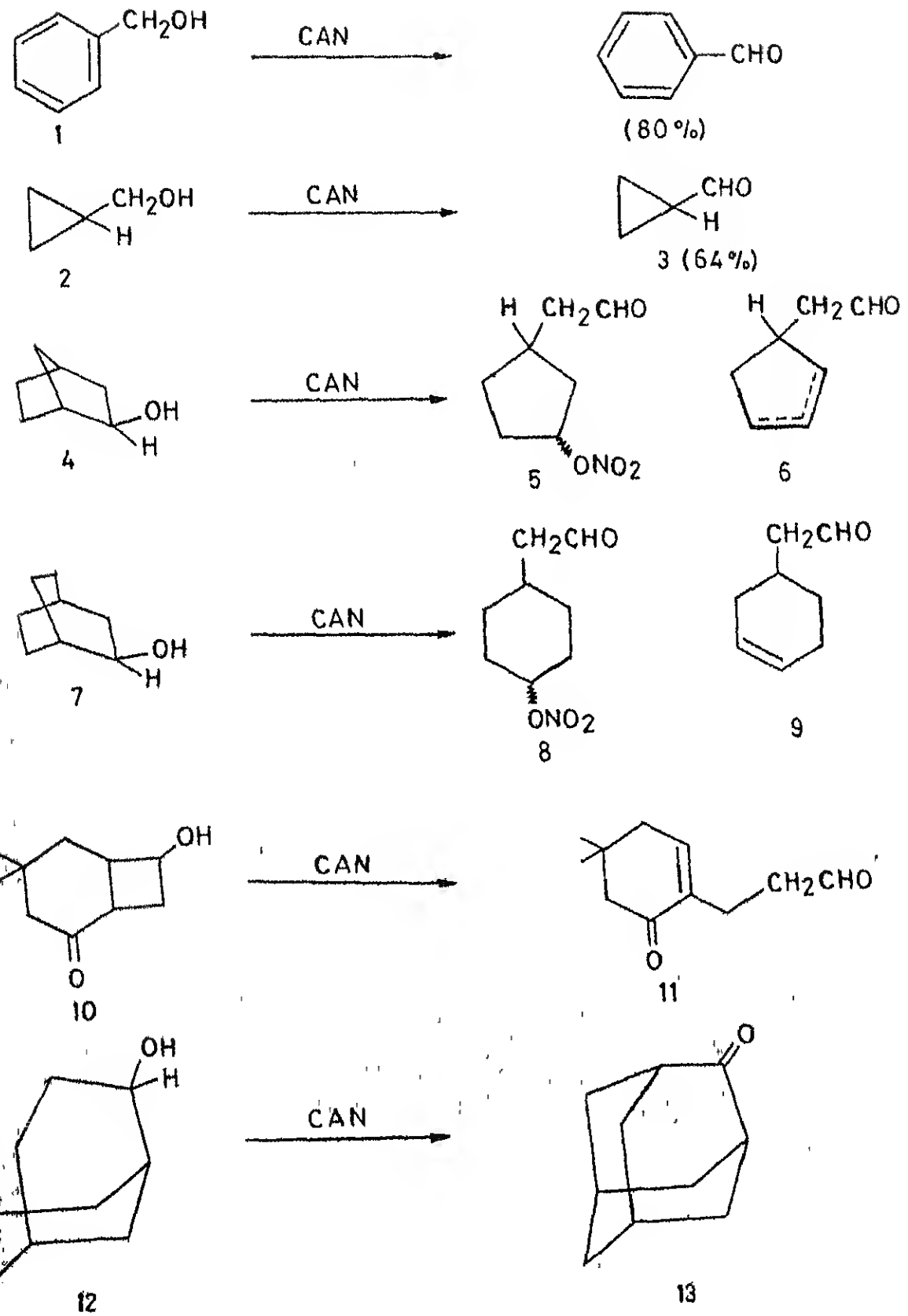
Ceric ion in its various coordination states has been known as a strong oxidising agent for many decades.[1] However, early use of ceric ion in organic chemistry was primarily restricted to colorimetric and quantitative estimation of alcohols.[2] Later studies[1] revealed the ability of ceric ion to oxidise a variety of organic functional groups but these efforts were mostly devoted to the studies of reaction kinetics and little, if any, effort was expanded to the preparative aspects of these reactions. Investigations during the last decade by Trahanovsky[3] and others[4] on ceric ammonium nitrate (CAN) and ceric ammonium sulphate (CAS) oxidation of a number of organic compounds have

drawn attention to the synthetic versatility of ceric ion in preparative organic chemistry.[4] Consequently, a great deal of promising synthetic methodology has been realised[4] employing ceric ions. In the following text the oxidation of common organic functional groups with ceric reagents is discussed.

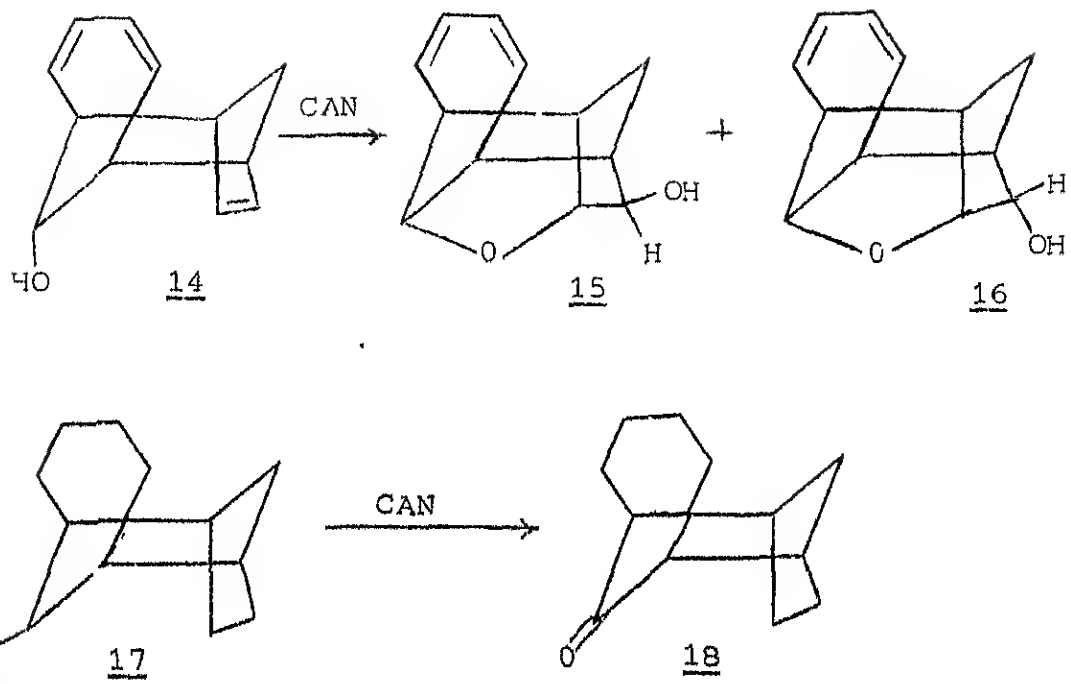
Alcohols:

Among the various functional groups, alcohols are most readily oxidised by ceric ion and their reactions have been extensively studied. Thus, benzylic[5] and cyclopropyl carbinyl[6] alcohols are oxidised to corresponding aldehydes. Bridged alcohols and cyclobutanols[8] are oxidised with adjacent C-C bond fission. α-Glycols are cleaved[9] by ceric ion and alkanols possessing a δ-hydrogen atom such as n-pentanol,[10] produce tetrahydrofuran derivatives in analogy with lead tetra-acetate oxidations. Simple cyclic alcohols like cyclopentanol and cyclohexanol as well as admantanol are dehydrogenated[11] to the corresponding ketones in the presence of ceric ion. These reactions with typical illustrations are depicted in scheme III.1. Mechanistic studies[8,12] have suggested that ceric ion induced alcohol cleavage is an one electron process, whereas for ketone formation a two electron oxidation is operative. The cyclization of bridged secondary alcohols[17] with ceric ammonium nitrate is shown in scheme III.2. Aryl methanols on treatment with sodium bromate and catalytic amount of ceric ammonium nitrate[14] give the

SCHEME III.1


CH2OH
CAN
CHO
1
(80 %)
CH2OH
H
CAN
CHO
H
2
3 (64 %)
OH
H
4
CAN
H
CH2CHO
ONO2
5
H
CH2CHO
6
OH
H
7
CAN
CH2CHO
ONO2
8
CH2CHO
9
OH
O
10
CAN
CH2CHO
O
11
OH
H
12
CAN
O
13

Scheme III.2

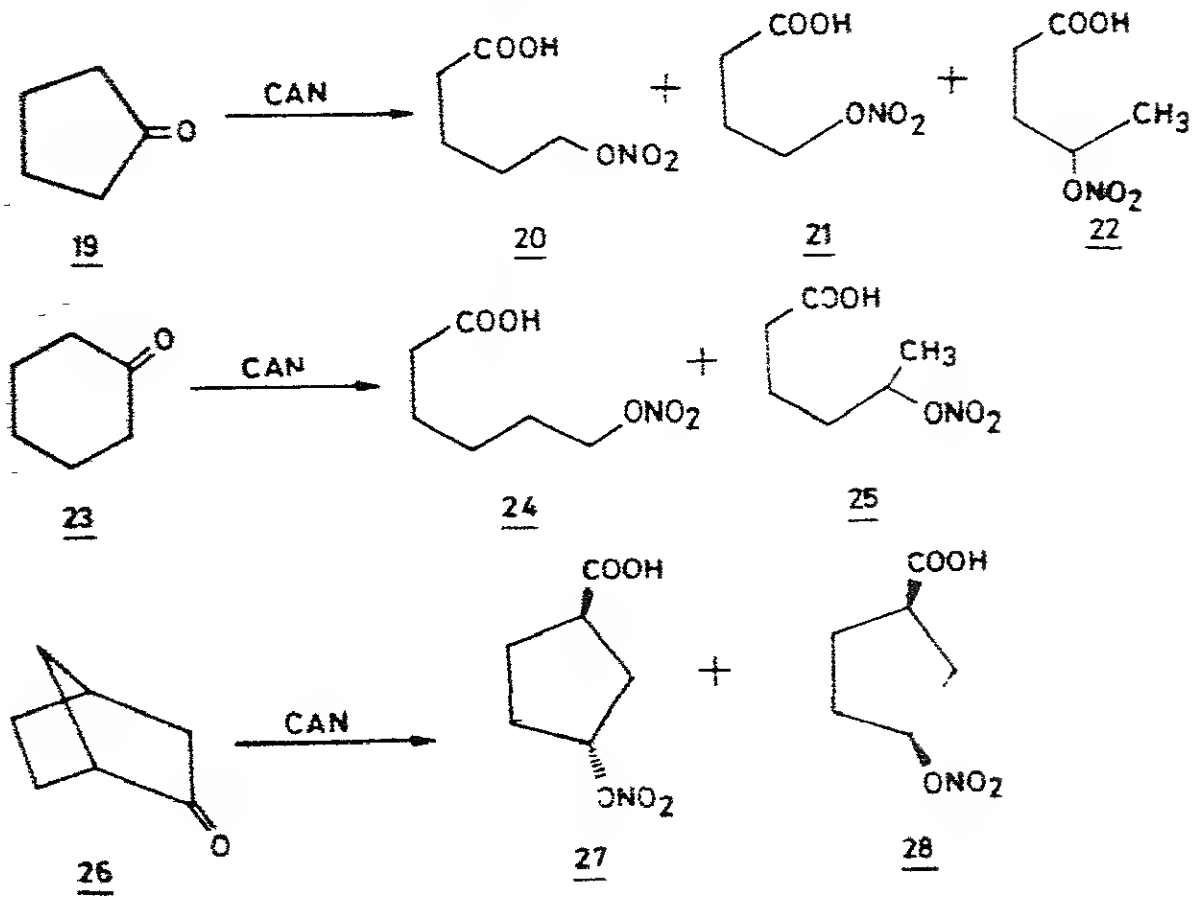


corresponding carbonyl compounds. Ceric ammonium nitrate absorbed on activated charcoal has been found[15] to be an effective catalyst for the air oxidation of benzyl alcohols and acyloins to the corresponding carbonyl compounds.

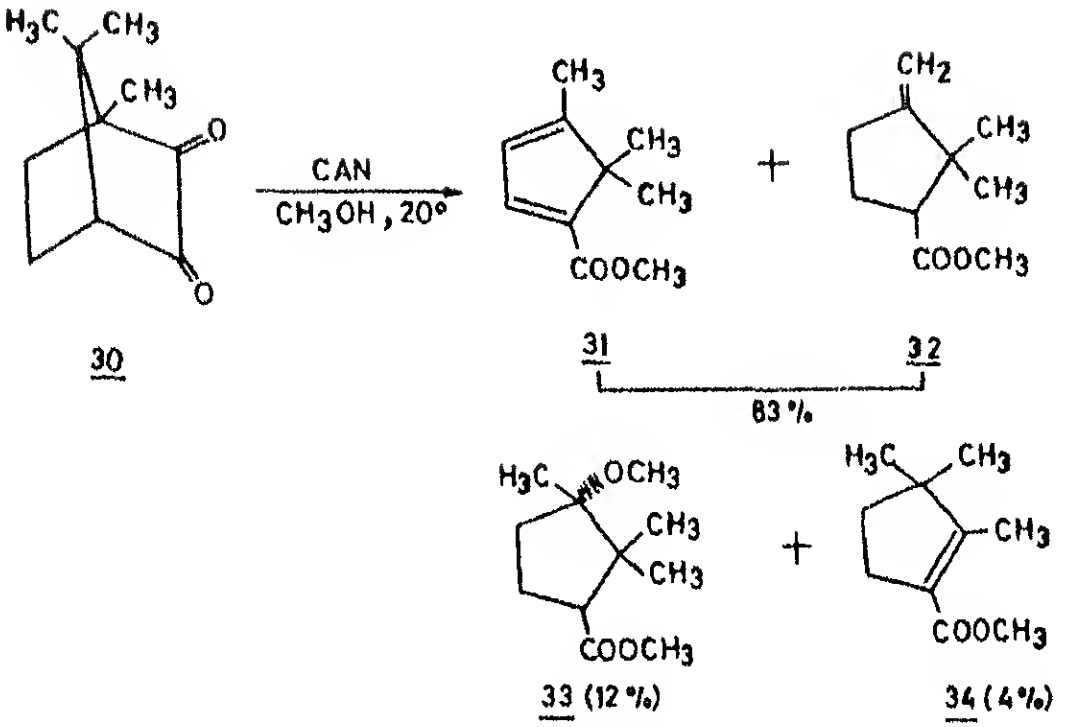
Carbonyl compounds:

Alicyclic ketones are rapidly consumed by ceric ammonium nitrate or ceric ammonium sulphate to furnish the corresponding ω-nitratocarboxylic acid *via* a pathway involving α-cleavage.[16] Cyclopentanone, cyclohexanone and norbornanone belong to this category and furnish mixtures of ring opened carboxylic acids (Scheme III.3). Camphor itself is not affected by treatment with

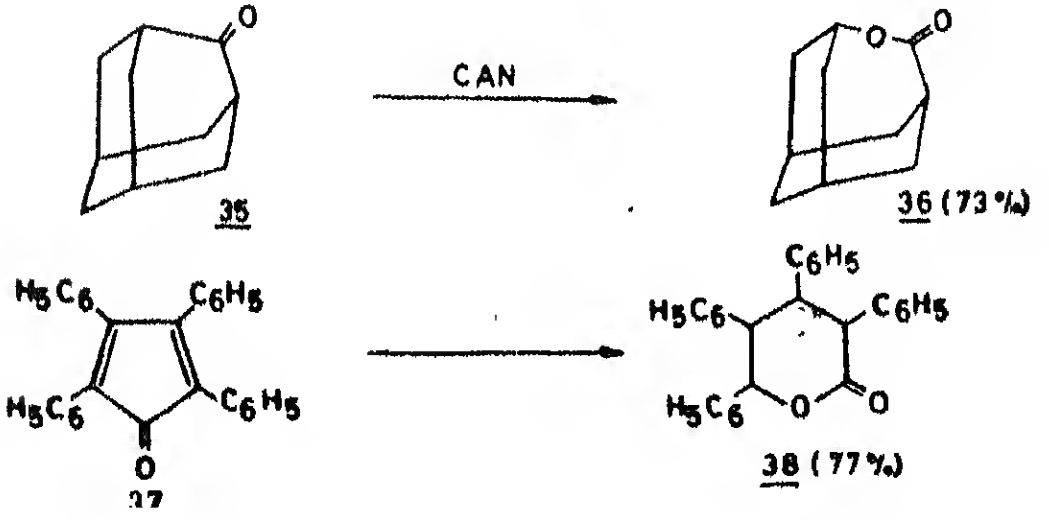
SCHEME III.3



SCHEME III.4

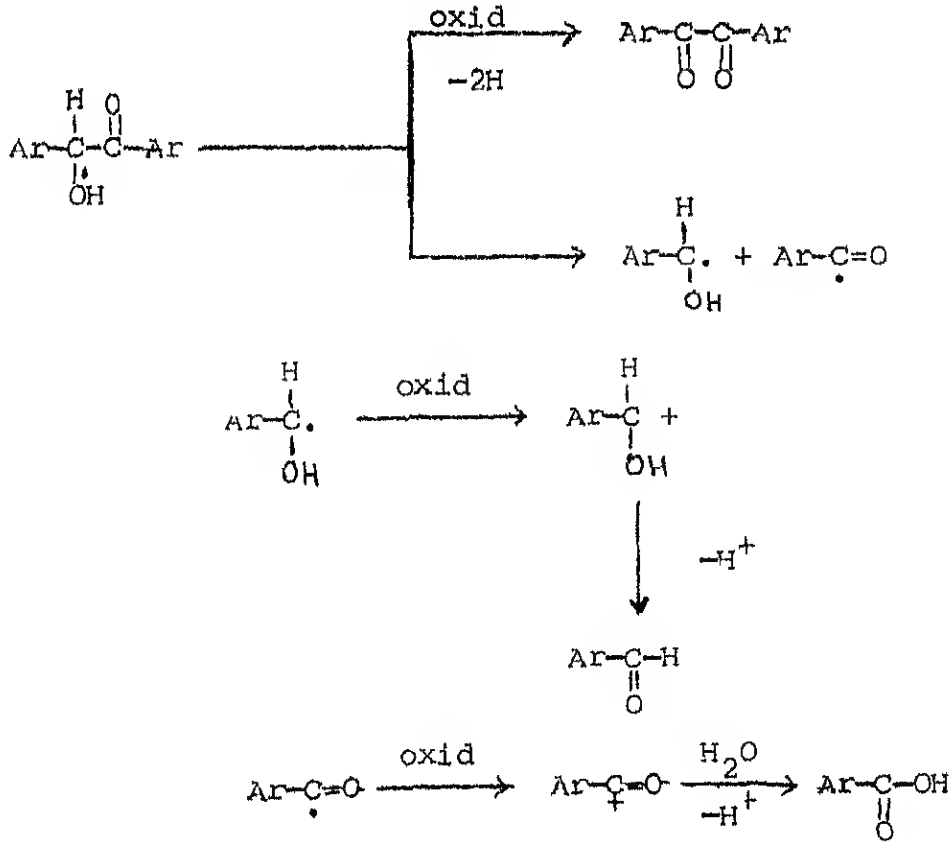


SCHEME III.5



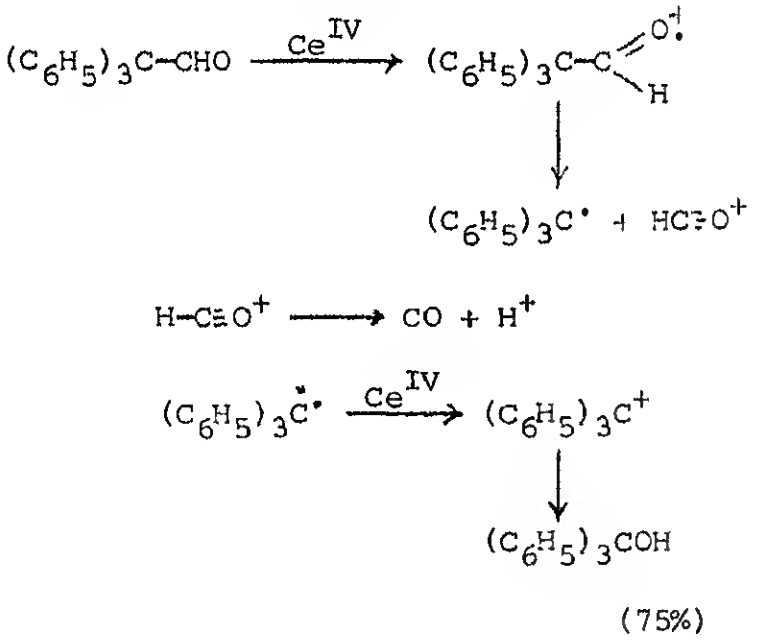
CAN in methanol at 20°, but the nonenolizable camphorquinone 70 is oxidized easily, mainly to an inseparable mixture of 31 and 32[17] (Scheme III.4). Adamantanone (35) and tetracyclone (37) exhibit unexpected behaviour towards CAN and undergo efficient Baeyer-Villiger oxidation[16,4] to the lactone (36) and tetraphenyl α-pyrone (38) (Scheme III.5). Benzoin[17] splits into benzaldehyde and benzoic acid (yield: 86%) when treated with CAN in aqueous-acetonitrile (vide Scheme III.6).

Scheme III.6



Aldehydes and Ketones[17] are susceptible to ceric ion oxidation. Formaldehyde, for example, is oxidized to formic acid (in acid media). It was reported that the reaction with triphenylacetaldehyde gave triphenyl carbinol together with some unreacted aldehyde, and the reaction was interpreted as proceeding via hydrogen abstraction (vide infra).

Scheme III.7

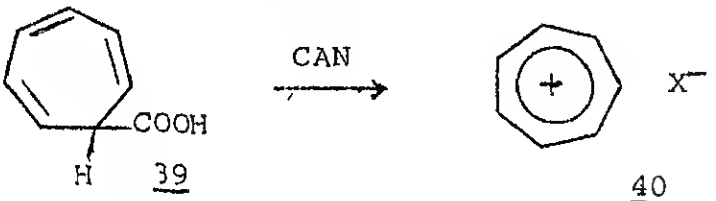


Carboxylic acids:

Simple aliphatic and aromatic carboxylic acids are usually stable towards ceric ion. However, oxalic acid[18] and malonic[19] acid are readily oxidized by ceric ion to carbon dioxide and water. The higher homologues of these dicarboxylic acids do not

react with ceric ion. Cycloheptatriene carboxylic acid 39 is readily decarboxylated to tropylium salt 40 with CAN in 30% yield[20].

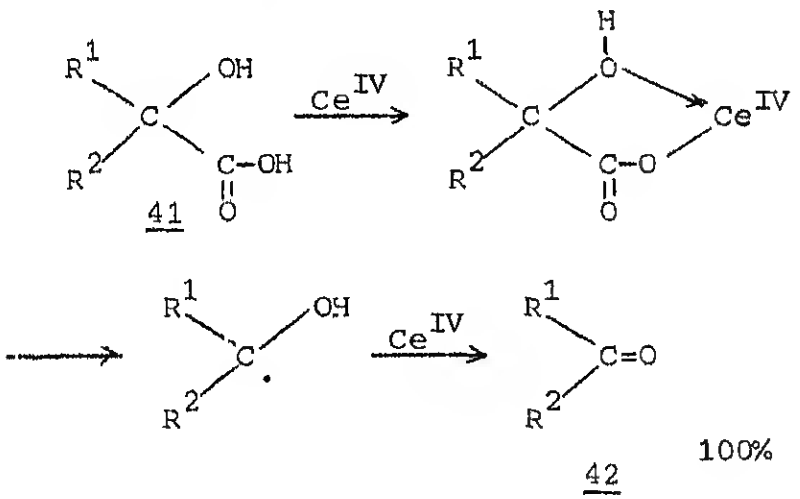
Scheme III.8



39 40

α-hydroxy carboxylic acids are degraded[21] to carbonyl compounds with loss of a carbon atom by ceric ion and this constitutes a useful degradative method.

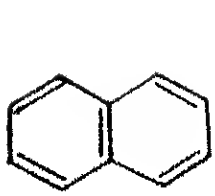
Scheme III.9



Hydrocarbons:

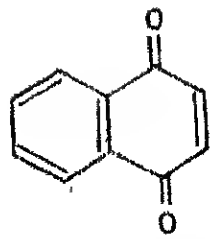
Aromatic hydrocarbons, possessing benzylic methyl and methylene groups, are rapidly oxidized to corresponding carbonyl functions by CAN in acidic medium[22]. Thus o-and p-xylenes are oxidized to

SCHEME III 10

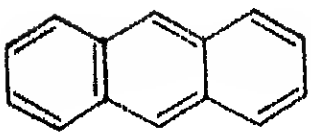


43

CAN

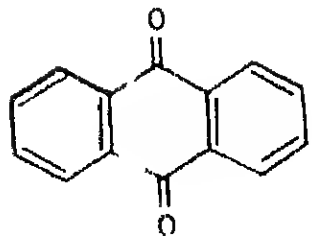


44 (73 %)

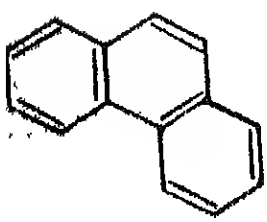


45

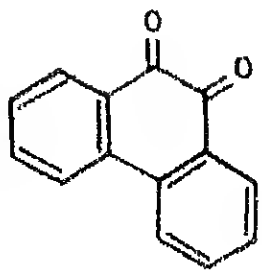
CAN



46

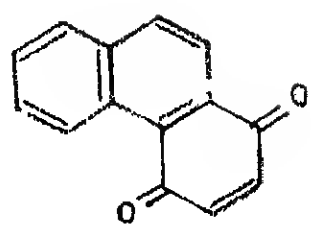


CAN



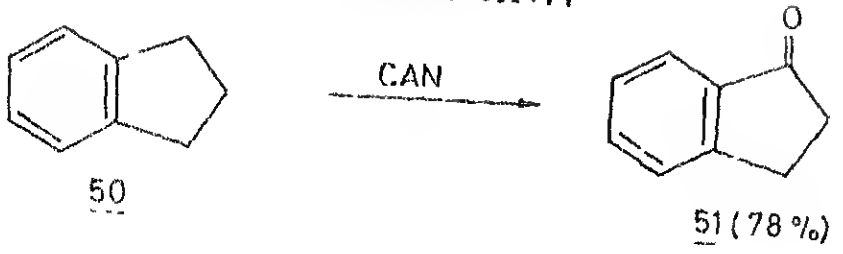
48

+

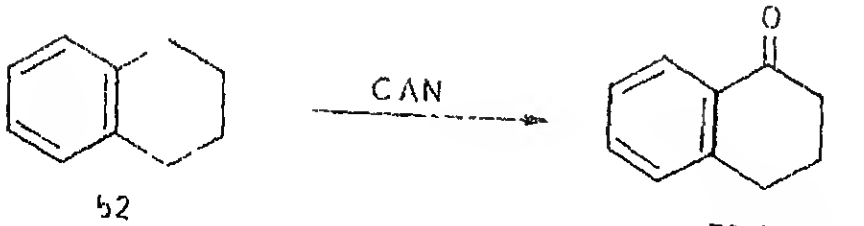


49

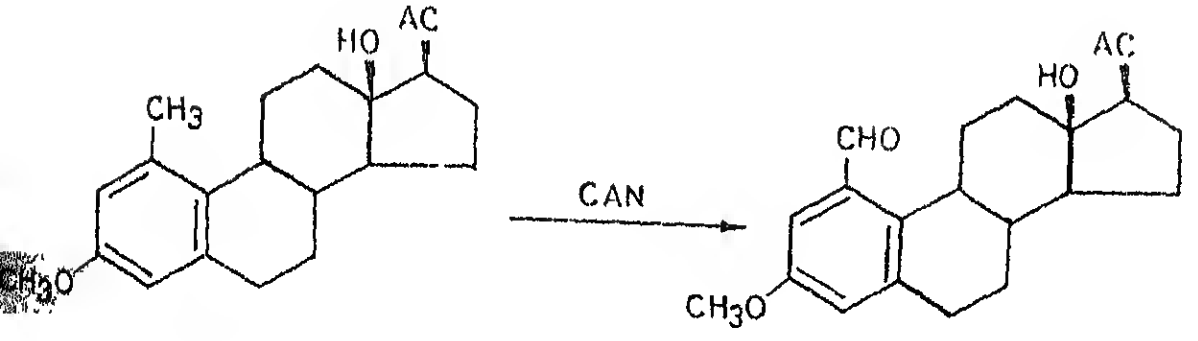
SCHEME III.11



50 → 51 (78 %)

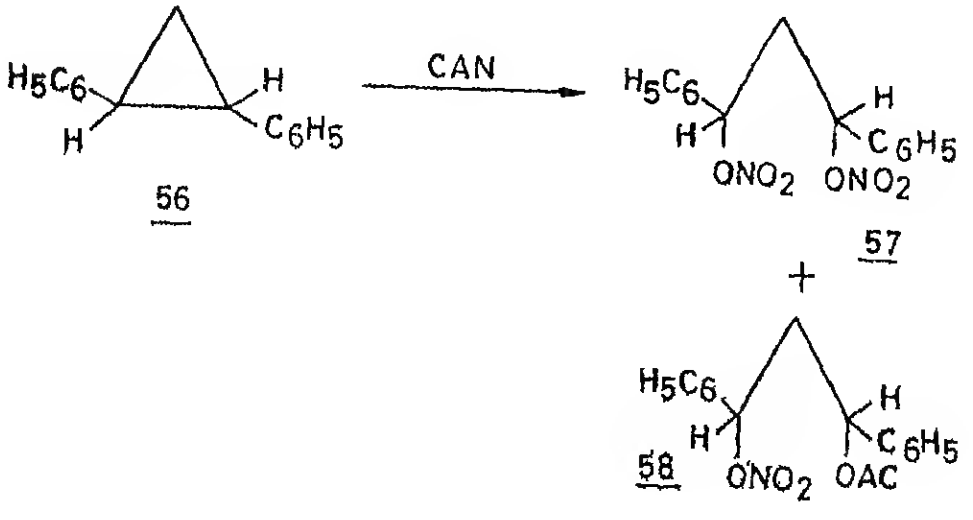


52 → 53 (76%)



54 → 55

SCHEME III.12



56 → 57 + 58

2- and 4-methyl-benzaldehydes respectively in 100% yield[18]. Polynuclear hydrocarbons are readily oxidized[23] to quinones by CAN under mild conditions and in reasonable yields (Scheme III.10).

Efficient conversion of indane 50 to 1-indanone 51, tetralin 52 to 1-tetralone 53 and steroidal[24] substrate 54 to 55 are useful examples of hydrocarbon oxidation (Scheme III.11). Aryl cyclopropanes like 56 are cleaved[25] by CAN in acetic acid to ring opened products 57 and 58 (Scheme III.12). Oxidation of 1,2-diaryl ethanes[26] with CAN produce only cleavage product: benzaldehyde, benzyl alcohol and benzyl nitrate (vide infra).

$$ArCH_2CH_2Ar \longrightarrow \underset{60\%}{ArCHO} + \underset{30\%}{ArCH_2OH} + \underset{10\%}{ArCH_2ONO_2}$$

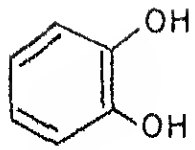
Hydroquinones:

Hydroquinones can be rapidly and efficiendly oxidized[27] to the corresponding quinones by CAN. This oxidation procedure is applicable for the generation of ortho-, para- and diquinones (Scheme III.13).

Oximes and semicarbazones:

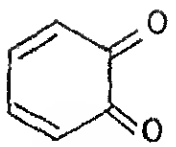
In many synthetic operations, it is expedient to either protect or purify carbonyl compounds via their oxime and semicarbazone derivative. CAN regenerates[28] the parent ketones or

SCHEME III.13

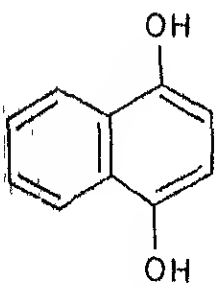


59

CAN

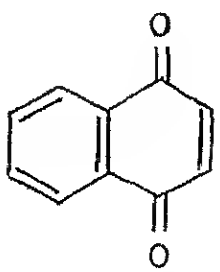


60 (83%)

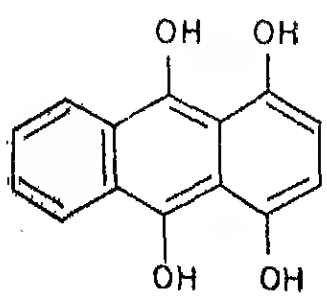


61

CAN

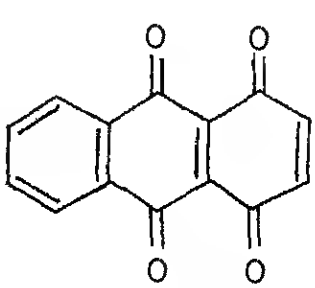


62 (88%)



63

CAN

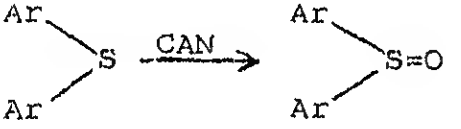


64 (89%)

aldehydes from oximes and semi-carbazones, at low temperature and in good yields and thus provides a superior and mild alternative to the conventionally used regeneration procedures.

Organo-sulphur compounds:

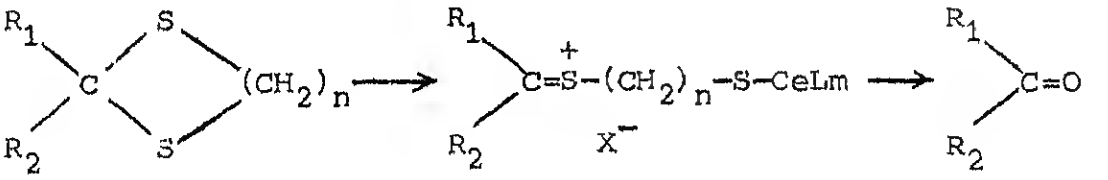
Diaryl sulphides are readily oxidized to the corresponding sulphoxides[25] in high yields without any contamination with the corresponding sulphones (vide infra).



65

The oxidation of sulphides to sulphoxides[29] can be carried out with catalytic amount of CAN and sodium bromate in acetonitrile[30]. 1,3-dithiolanes and dithianes are readily degraded to their parent carbonyl compounds[31] on treatment with CAN. The reaction may be visualized to take place as shown.

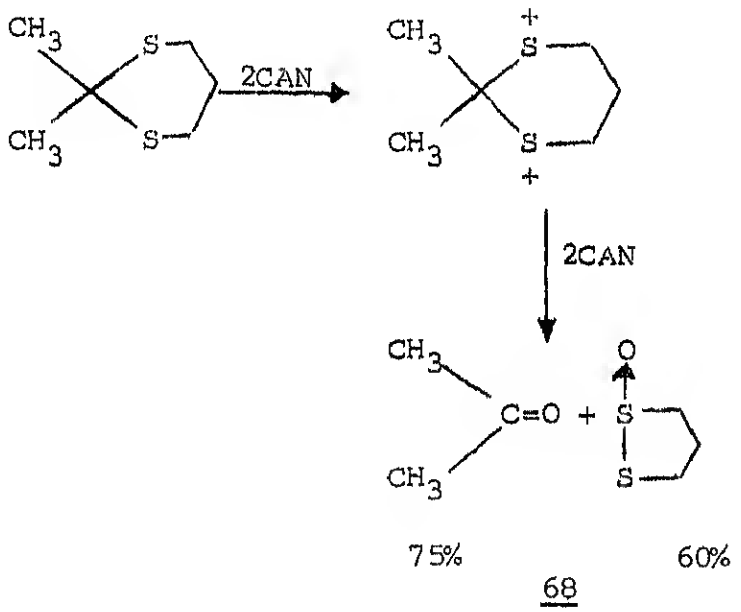
Scheme III.14



66

The cleavage of 1,3-dithianes by ceric ammonium nitrate[32] requires four equivalents of the salt for high yields because of the following mechanism.

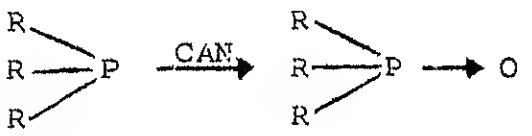
Scheme III.15



68

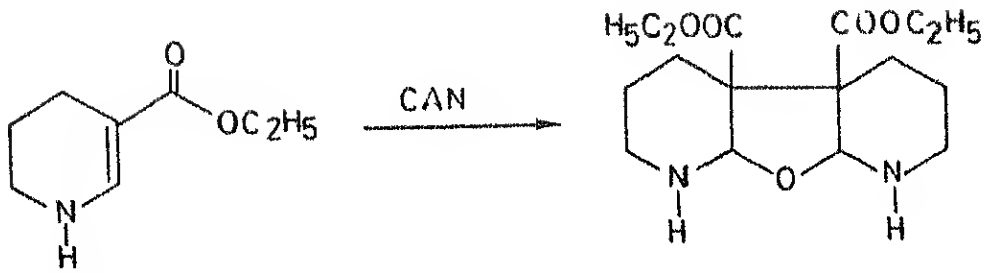
Miscellaneous compounds:

Phosphines are quantitatively transformed to the corresponding phosphine oxides by ceric ion.[4] (vide infra).



69 70

SCHEME III.16

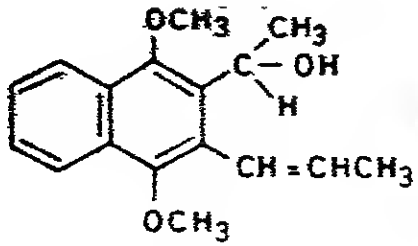


71 72

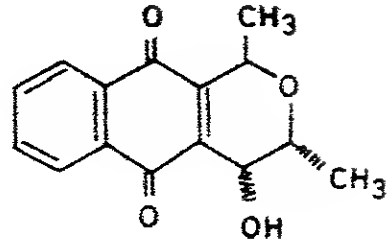
SCHEME III.17

73 74

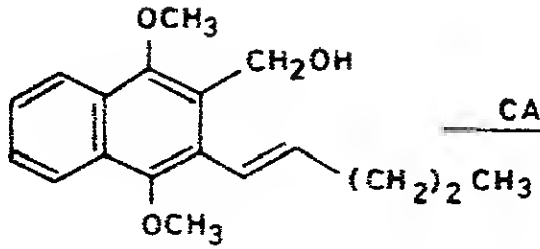
SCHEME III.18



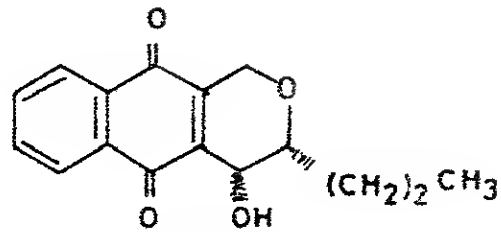
75



76

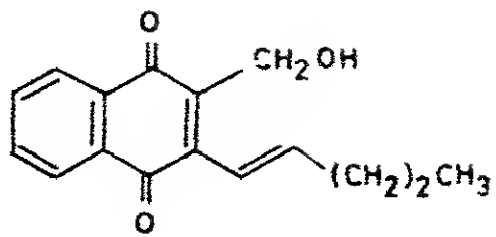


77



78 (54%)

+

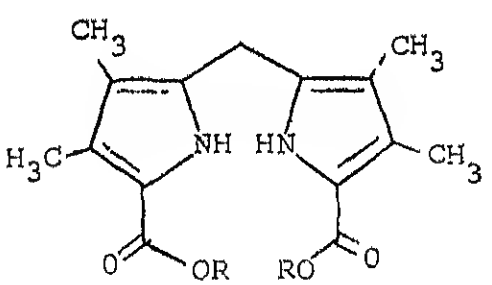


79 (29%)

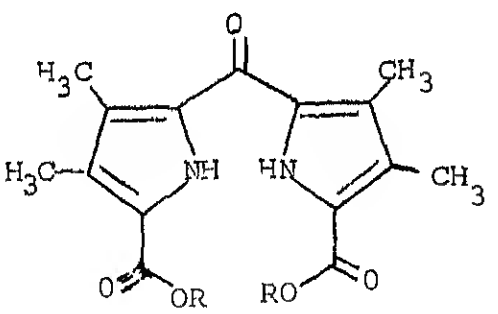
Oxidation of ethyl-1,4,5,6-tetranydronicotinate[33] (71) with CAN gives furodipiperidine ring system (72) (Scheme III.16). Ceric ammonium nitrate in aqueous acetonitrile oxidises[34] a variety of hydroquinone dimethyl ethers to the corresponding quinones in high yield (Scheme III.17).

The dimethoxynapthalenes 75 and 76 undergo oxidative cyclization with CAN[35] (Scheme III.18). Ceric ammonium nitrate in aqueous acetic acid (buffered with sodium acetate) rapidly oxidises[36], 2,2'-dipyrrylmethanes to the corresponding 2,2'-dipyrrylketones.

Scheme III.19



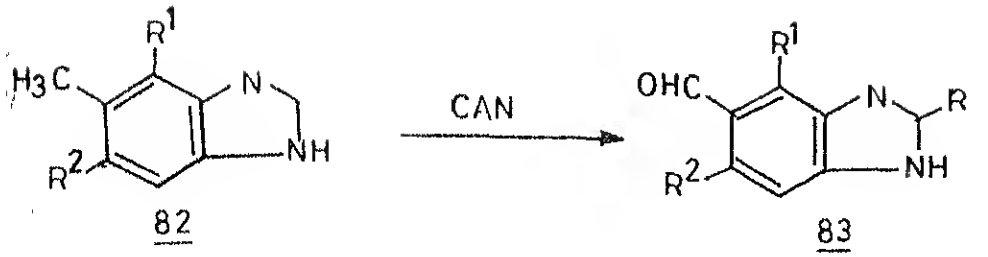
80



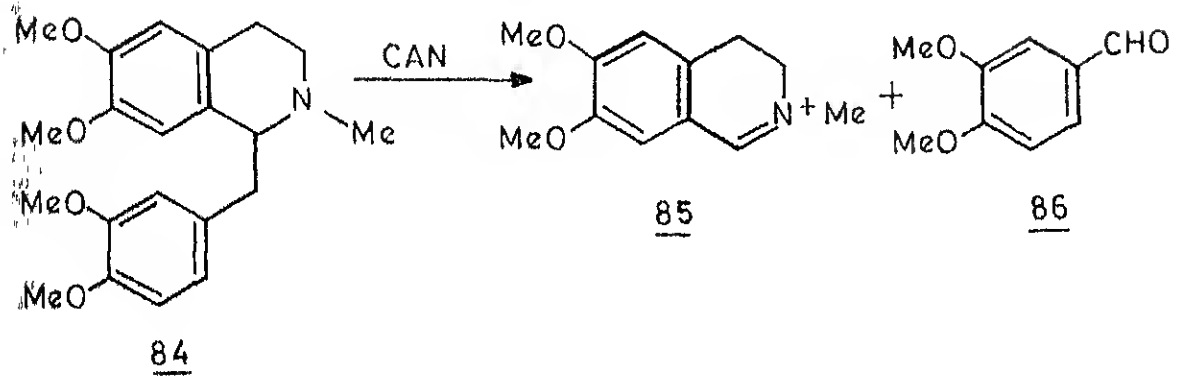
81

Methylbenzimidazoles are oxidised by CAN to give 25-60% yield of benzimidazole carboxaldehyde[37] (Scheme III.20). Laudanosine (84) is oxidised[38] by CAN to veratraldehyde and the dihydroisoquinolinium salt 85 (Scheme III.21). The sodium salts 87 and 89 undergo coupling reaction[39] with ceric ammonium nitrate (Scheme III.22).

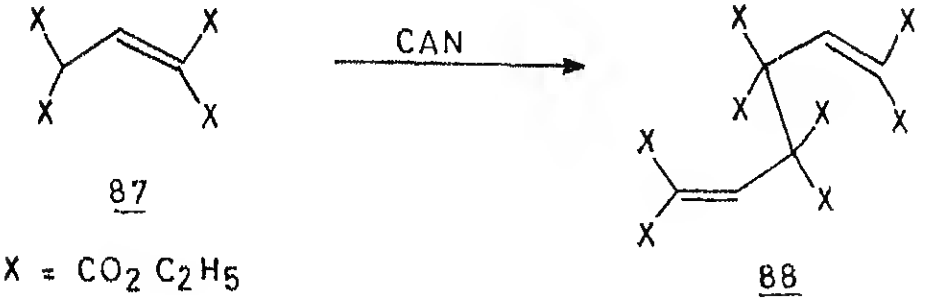
SCHEME III.20

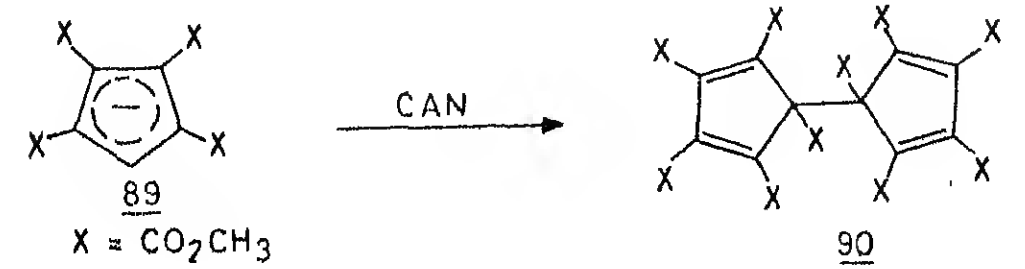


SCHEME III 21

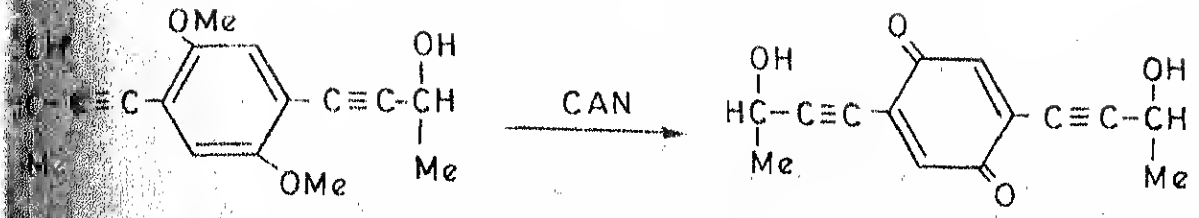


SCHEME III.22

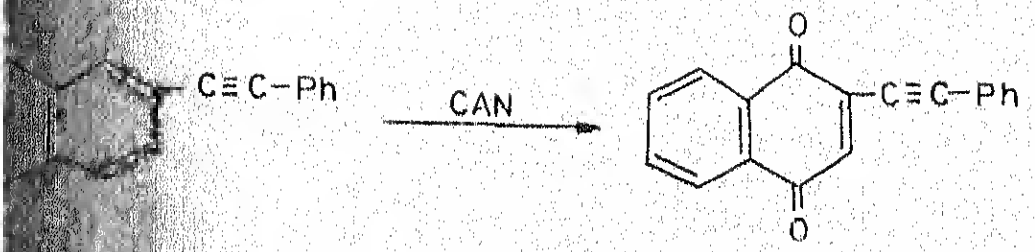




SCHEME III.23

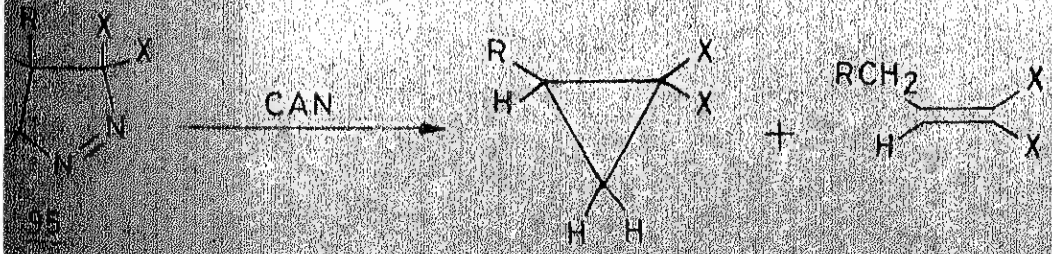


91 92



93 94

SCHEME III.24



95 96 97

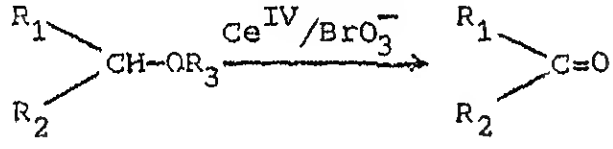
CO_2Me

CO_2Me, Et, etc.

Compound 91 and 93 undergo ceric ammonium nitrate oxidation to yield 92 and 94 respectively.[40] (Scheme III.23). Reactions of pyrazolines 95 with CAN in acetone at 0^{o} give exclusively the corresponding cyclopropane or the mixture of cyclopropane and olefin[41] (Scheme III.24).

Sodium bromate and catalytic amount of ceric ammonium nitrate oxidise ethers to carbonyl compounds[42] (vide infra).

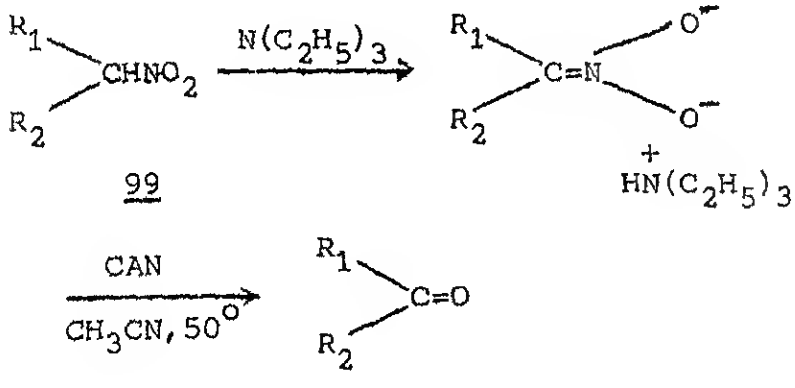
Scheme III.25



98

The transformation of $>\!-NO_2 \longrightarrow >\!C=O$ can be conducted by treatment of nitro compounds with CAN and triethylamine.[43] (vide Scheme III.26).

Scheme III.26



99

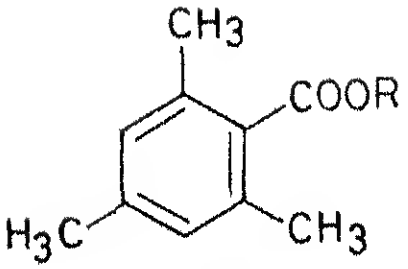
Surprisingly no work has been reported in respect of the reaction of CAN with ethers, aldazines, pyrazoles, 2-pyrazolin-5-ones and 1,2,3,4-tetrahydro-carbazole. It was, therefore, desirable to study the CAN oxidation of these substrates.

Various reagents[44-46] have been developed for effecting cleavage of the alkyl oxygen bond of methyl esters by nucleophilic displacement of the carboxylate anion from the methyl group viz., lithium iodide in refluxing pyridine, 2,6-lutidine, or 2,4,6-collidine,[44] lithium iodide in hot dimethyl-formamide (DMF)[45] and potassium t-butoxide in warm dimethyl sulphoxide[46].

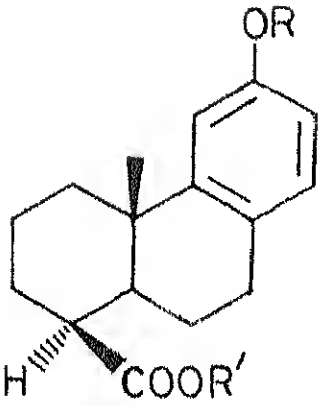
Lithium thiopropoxide, sodium thioethoxide and sodium thianethoxide have also been shown to be effective reagents for the cleavage of nindered esters.[47-51] Treatment of esters[50-51] 100 and 101 with sodium thiomethoxide at 25° for 2 hr affords the corresponding acids 101 and 102 each in 98% yield (Scheme III.27).

S_N2-type cleavages of esters and lactones with phenyl selenide[52-53] anion have been studied. This reagent has been found to be extremely potent nucleophile. Valerolactone on treatment with sodium phenyl selenide in THF/HMPA at reflux temperature for 3 hr, furnished ω-phenyl selenenyl carboxylic acid in 85% yield (Scheme III.28).

Scheme III.27



100



101

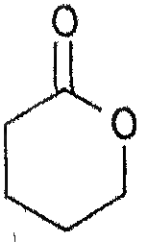
100 R = CH_3

102 R = H

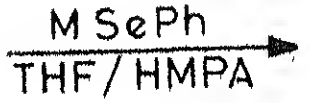
101 R = R′ = CH_3

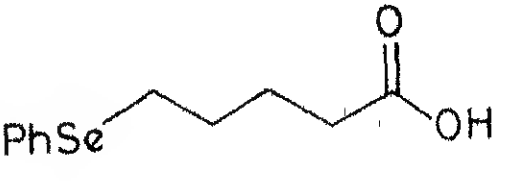
103 R = CH_3, R′ = H

Scheme III.28



104



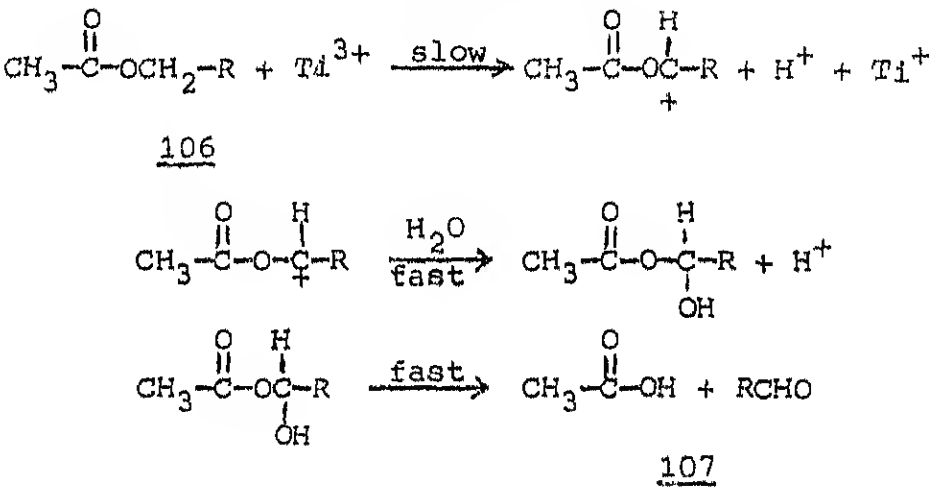


105

M = Li , Na

Oxidation of methyl, ethyl, n-propyl, iso-propyl, butyl acetates by Ti^{3+} in acetic acid-sulphuric acid mixture has been investigated.[54-57] (vide infra).

Scheme III.29



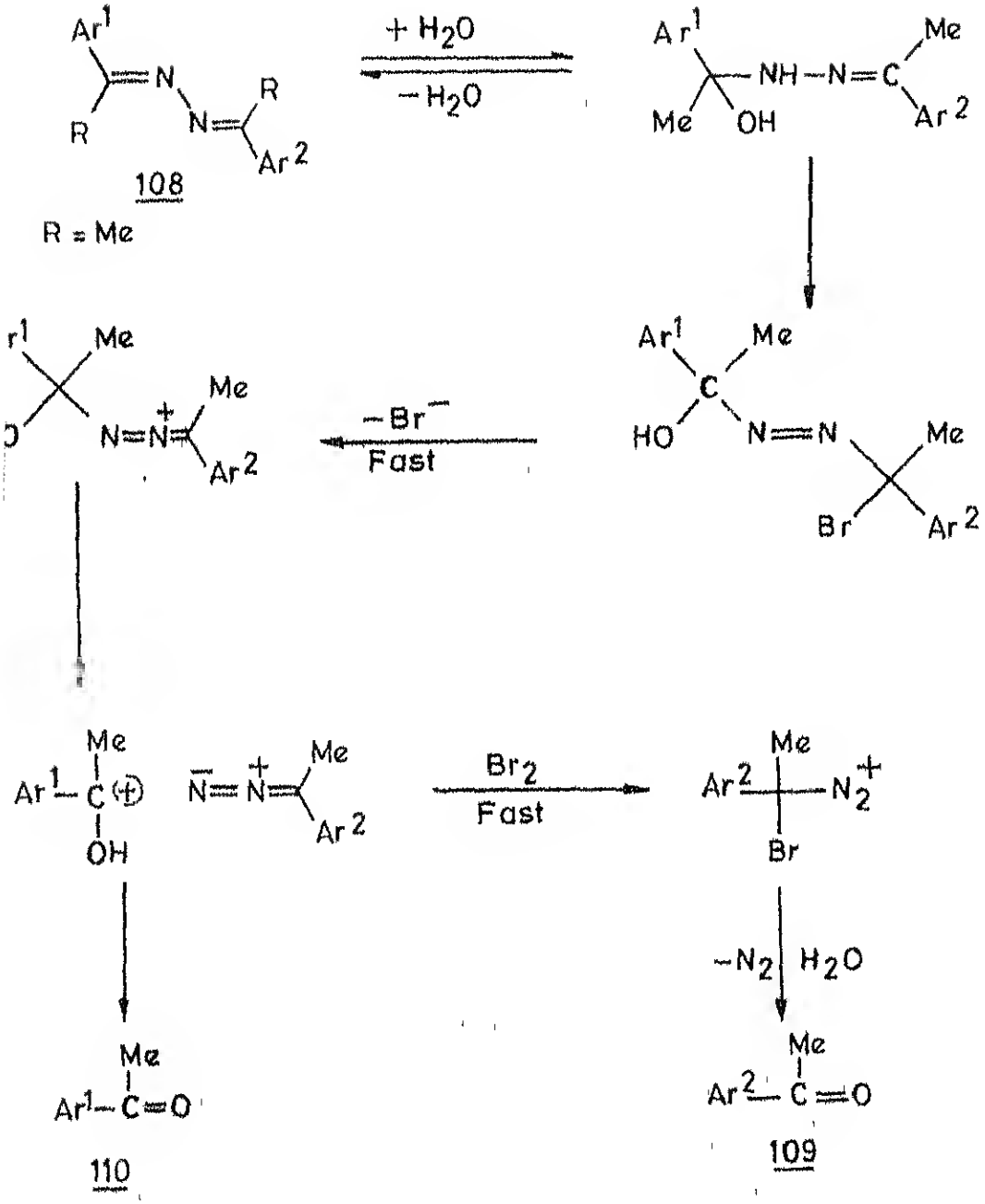
106

107

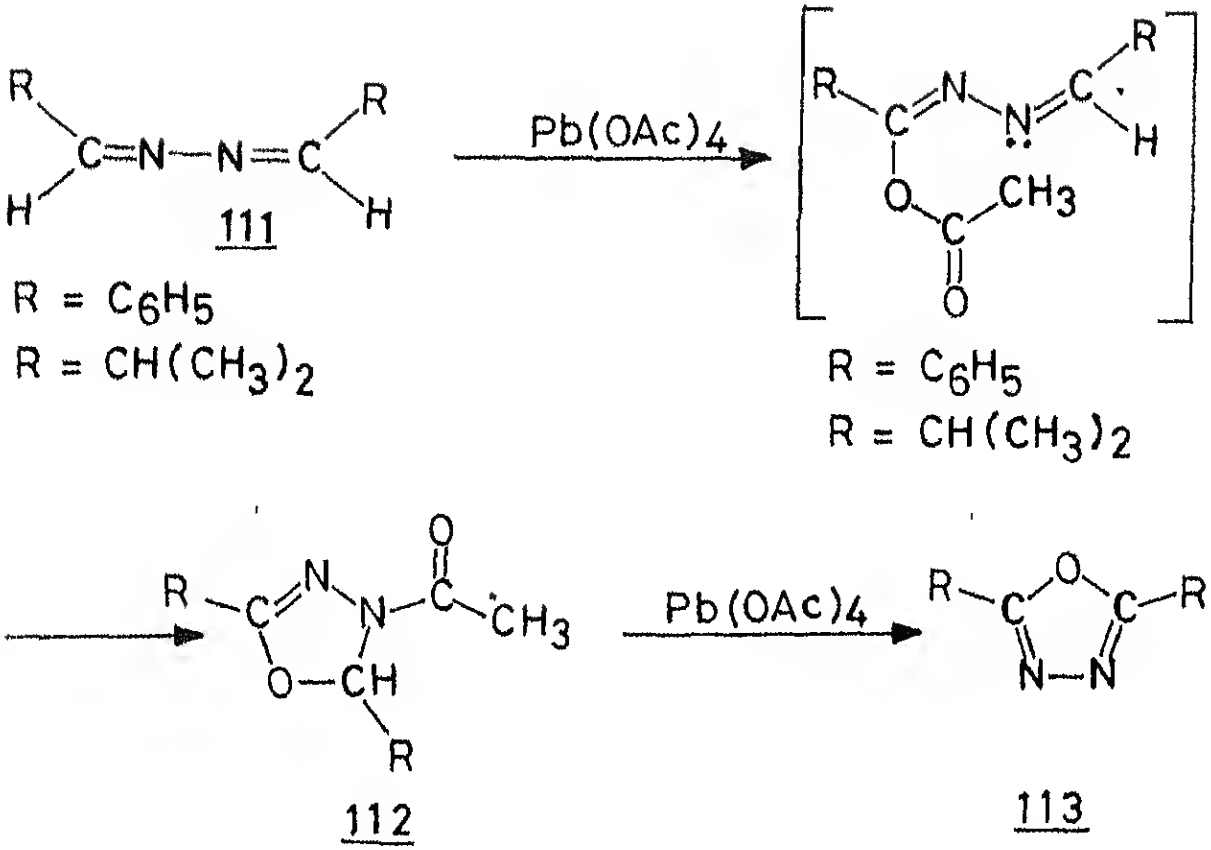
Oxidation of esters[57] by Cr^{VI} in acetic acid has been reported. The products are corresponding ketones, which are identified as their corresponding 2:4-dinitro-phenylhydrazones. Oxidation of esters by bromine and N-bromo-succinimide[56] has been studied leading to the formation of corresponding acids. On the other hand, the oxidation of benzyl esters with bromine and N-bromosuccinimide produced the corresponding benzaldehydes.

Oxidation of esters have also been investigated with triphenyl-dibromo-phosphorane, leading to the formation of corresponding acids, which were identified by comparison with authentic samples (ir, nmr).

SCHEME III.30



Scheme III.31



111

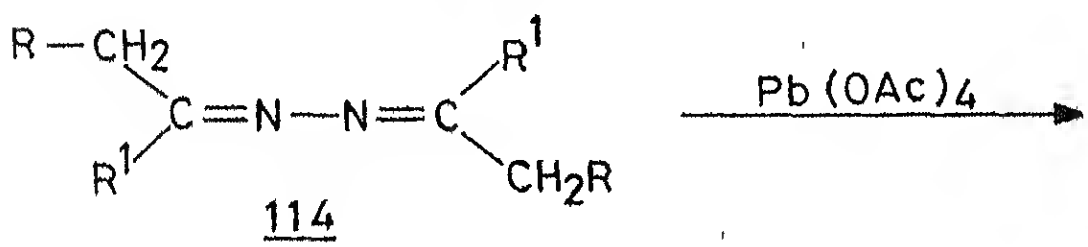
R = C_6H_5
R = $CH(CH_3)_2$

R = C_6H_5
R = $CH(CH_3)_2$

112

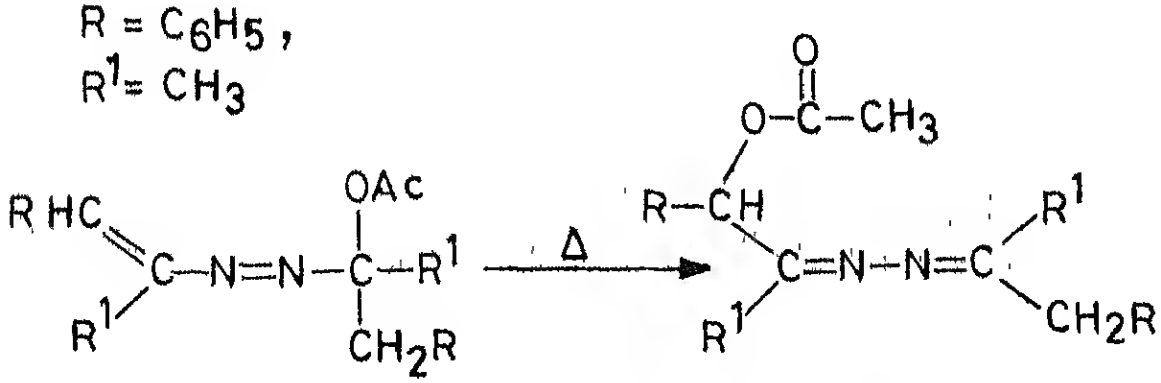
113

Scheme III.32



114

R = C_6H_5 ,
R^1 = CH_3



115

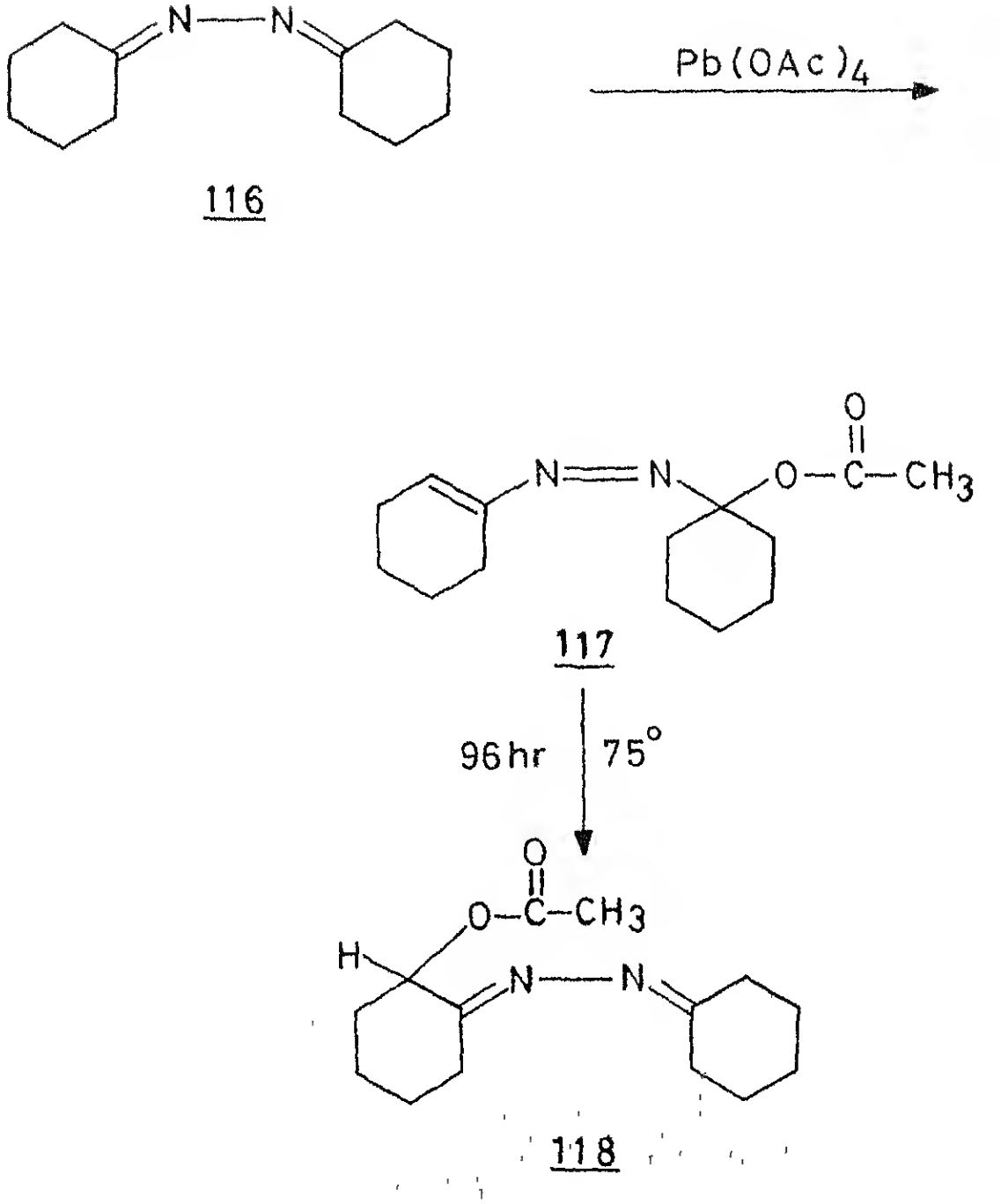
It seems probable that the ester reacts with triphenyl-dibromo-phosphorane to form an oxonium salt, which then undergoes cleavage through its reaction with bromide ion.

Azines[58] (2,3-diazabuta-1,3-dienes, R=Me or H) are smoothly cleaved by bromine in 7:3 acetic acid-water at 25° to give quantitative amounts of the corresponding substituted acetophenone(s) or benzaldehyde(s), with the evolution of nitrogen. A plausible mechanism of oxidative bromination of azines is suggested in Scheme III.30. The oxidation[59] of aldazines (RCH=N-N=CHR) with lead tetra-acetate has been found to yield 1,3,4-oxadiazolines when R=aryl or alkyl. 112 could be converted to the 1,3,4-oxadiazole (113) by further oxidation with lead tetra-acetate (Scheme III.31).

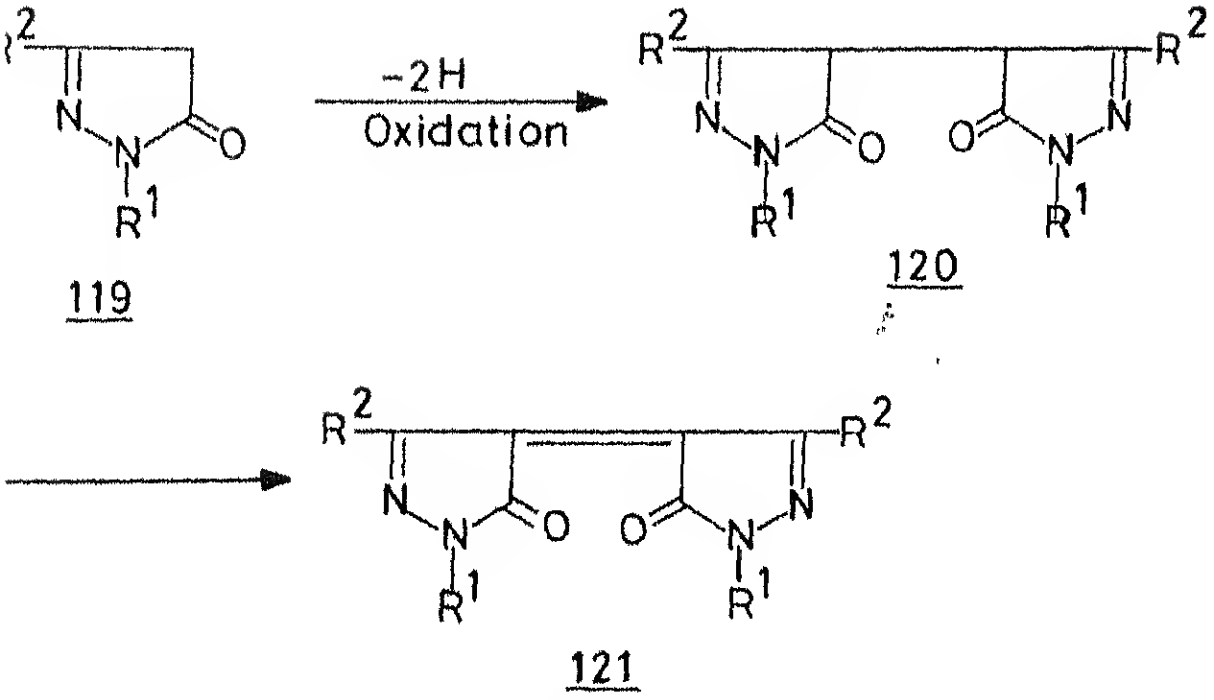
The oxidation of aliphatic ketazines with lead tetracetate has been found to give α,β-unsaturated azoacetates (Scheme III.32). Aromatic ketazines failed to react with lead tetracetate. α,β-unsaturated azoacetates 114 are stable when stored at low temperature but rearrange to α-acetoxy ketazines upon heating[59]. (Scheme III.32).

Treatment of cyclohexanoneazine with 1 equivalent of lead tetracetate resulted in the formation of α,β--unsaturated azo-acetates[59] (Scheme III.33). The hydrogen atom on C-4 of 2-pyrazolin-5-ones are readily attacked by mild oxidizing agents. The products of this reaction are bis-pyrazolinones, when phenylhydrazine or nitrous acid is used as the oxidizing agent[59-64]

Scheme III.33

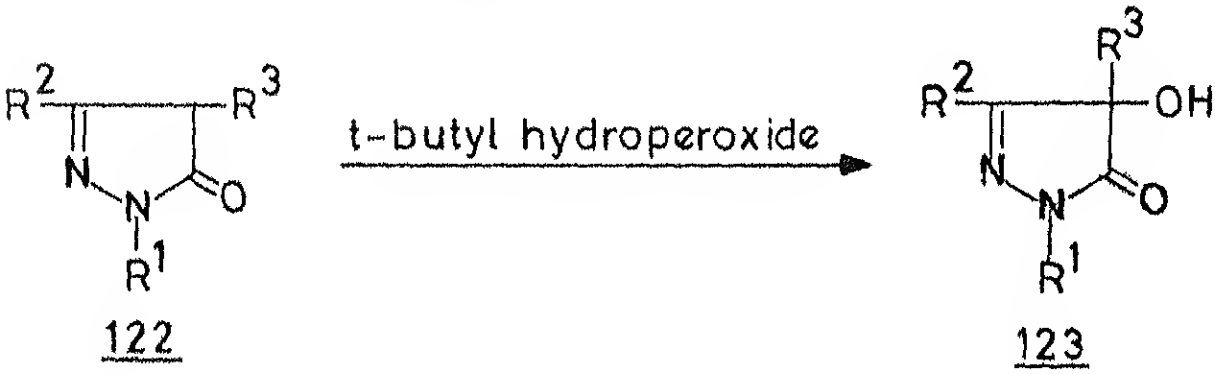


Scheme III.34



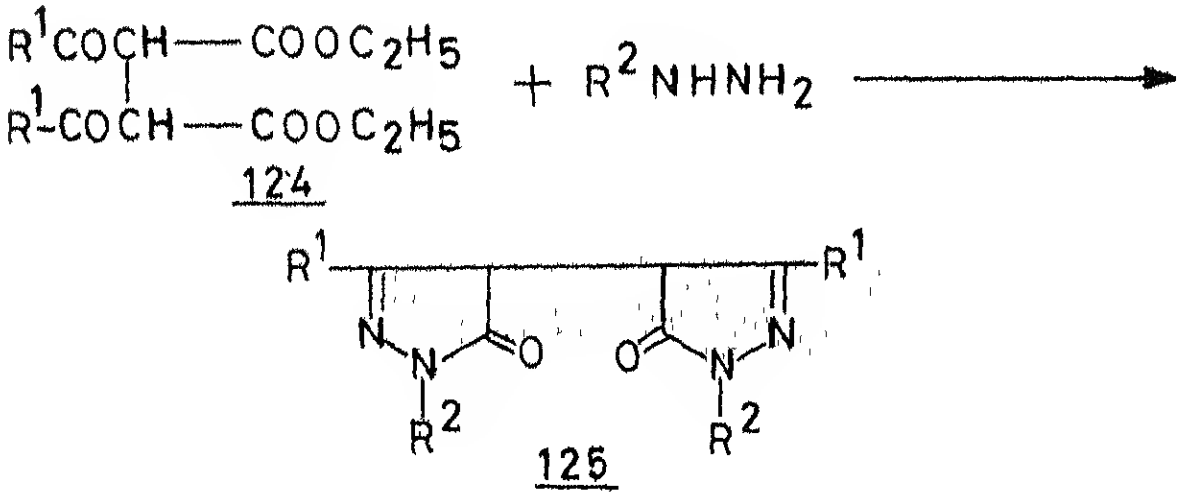
119 120 121

Scheme III.35



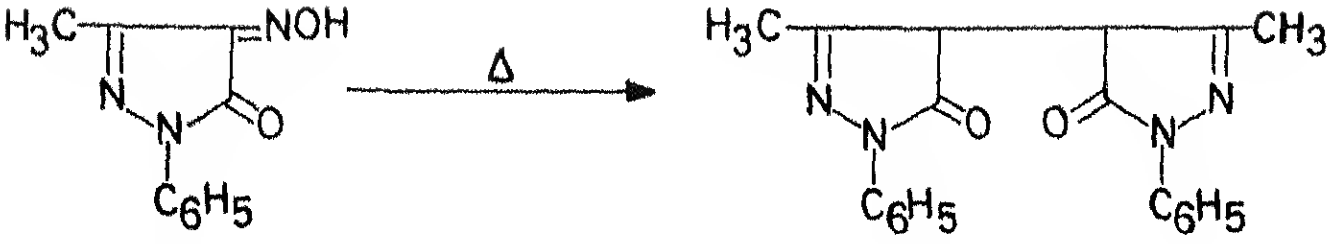
122 123

Scheme III.36



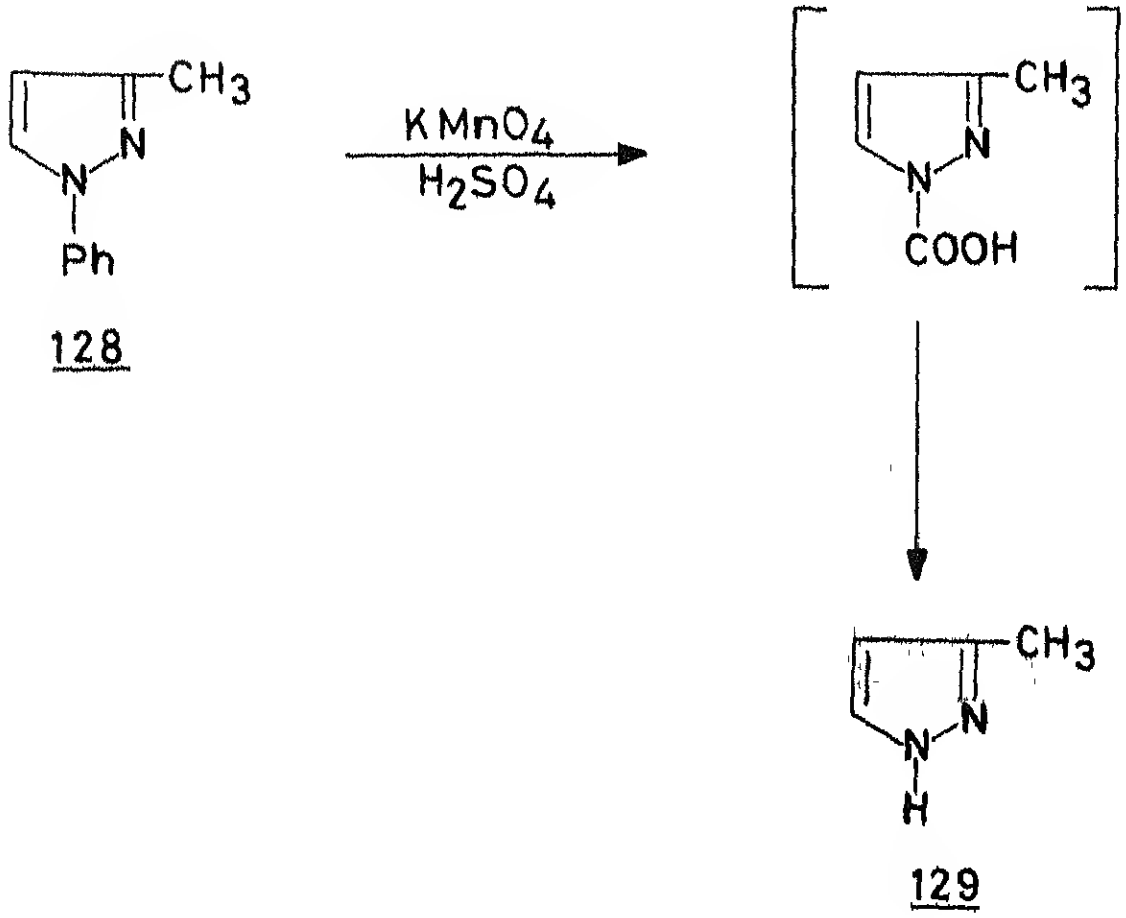
124 125

Scheme III.37



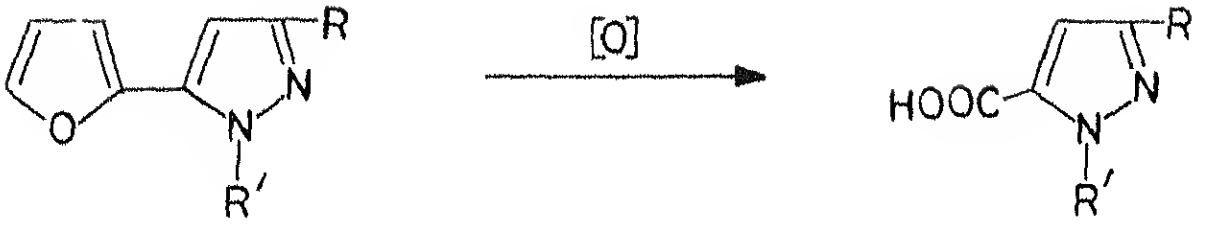
126 127

Scheme III.38



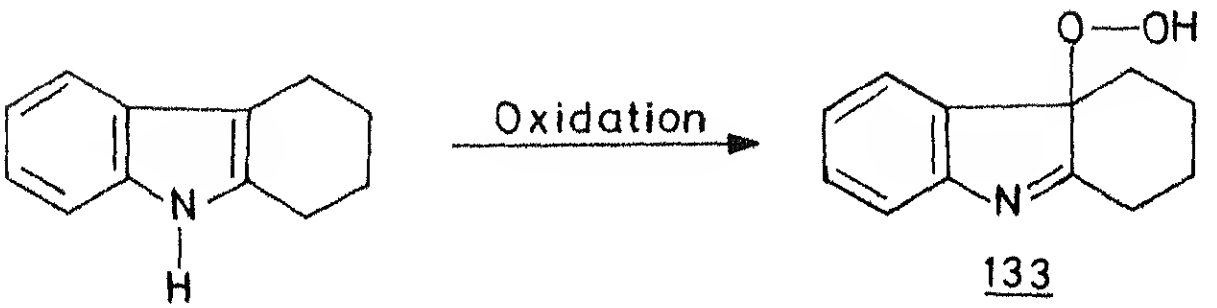
128 129

Scheme III.39

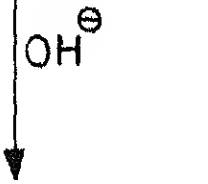


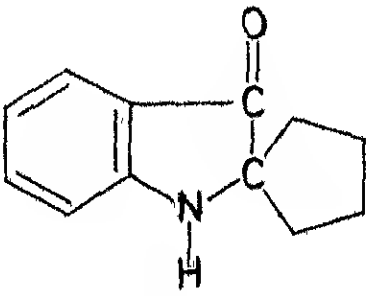
130 131

Scheme III.40



132 133





134

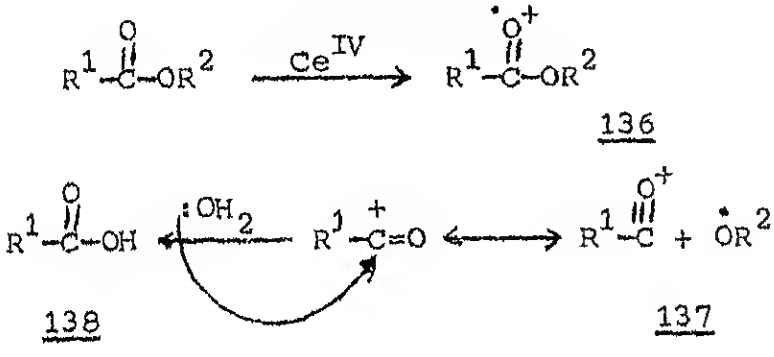
$KMnO_4$ in acid media oxidizes the benzene ring leaving a methyl group unchanged in the pyrazole nucleus[75] (Scheme III.38). The oxidation of 2-furyl-pyrazole with neutral permanganate has been studied. Only the furan ring is oxidized and alkyl or aryl substituents remain uneffected[76] (Scheme III.39). Chromic acid has also been used for the oxidation of pyrazoles.

Catalytic oxidation of 1,2,3,4-tetrahydro-carbazole gives 11-hydro-peroxytetrahydrocarbazolenine.[77-79] The latter compound on treatment with alkali yields the spiro compound (Scheme III.40).

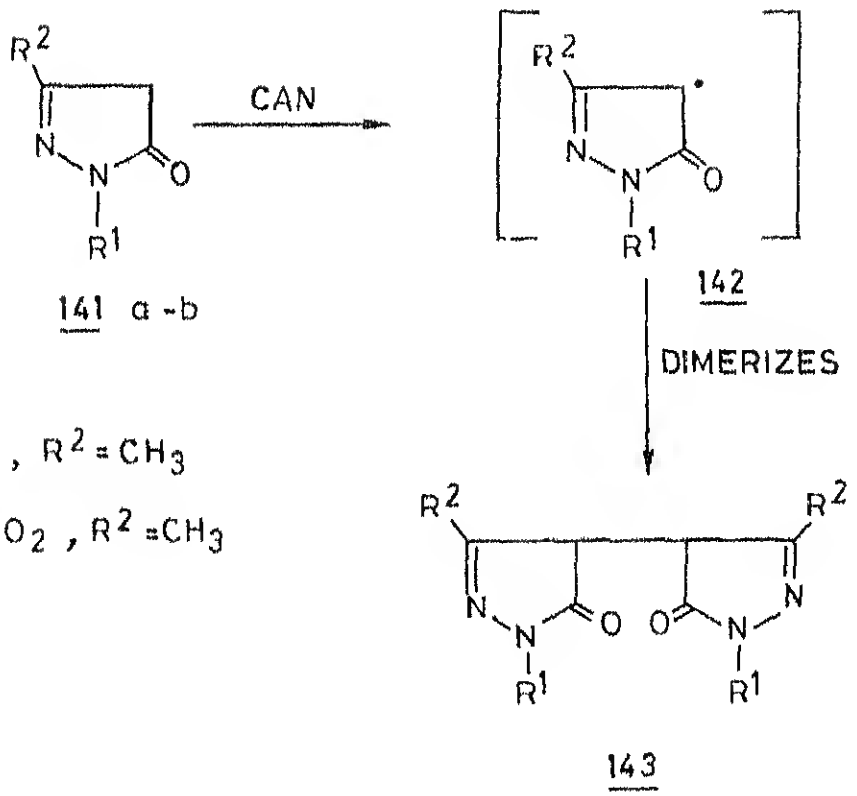
RESULTS AND DISCUSSION

Oxidative cleavage of esters (135a-r) with ceric ammonium nitrate has been studied (in 1:4 molar ratio) at reflux temperature 80° for 5-6 hr, resulting in the formation of their corresponding acids. The reaction is believed to proceed through the formation of free radicals (vide Scheme III.41).

Scheme III.41



SCHEME III.42



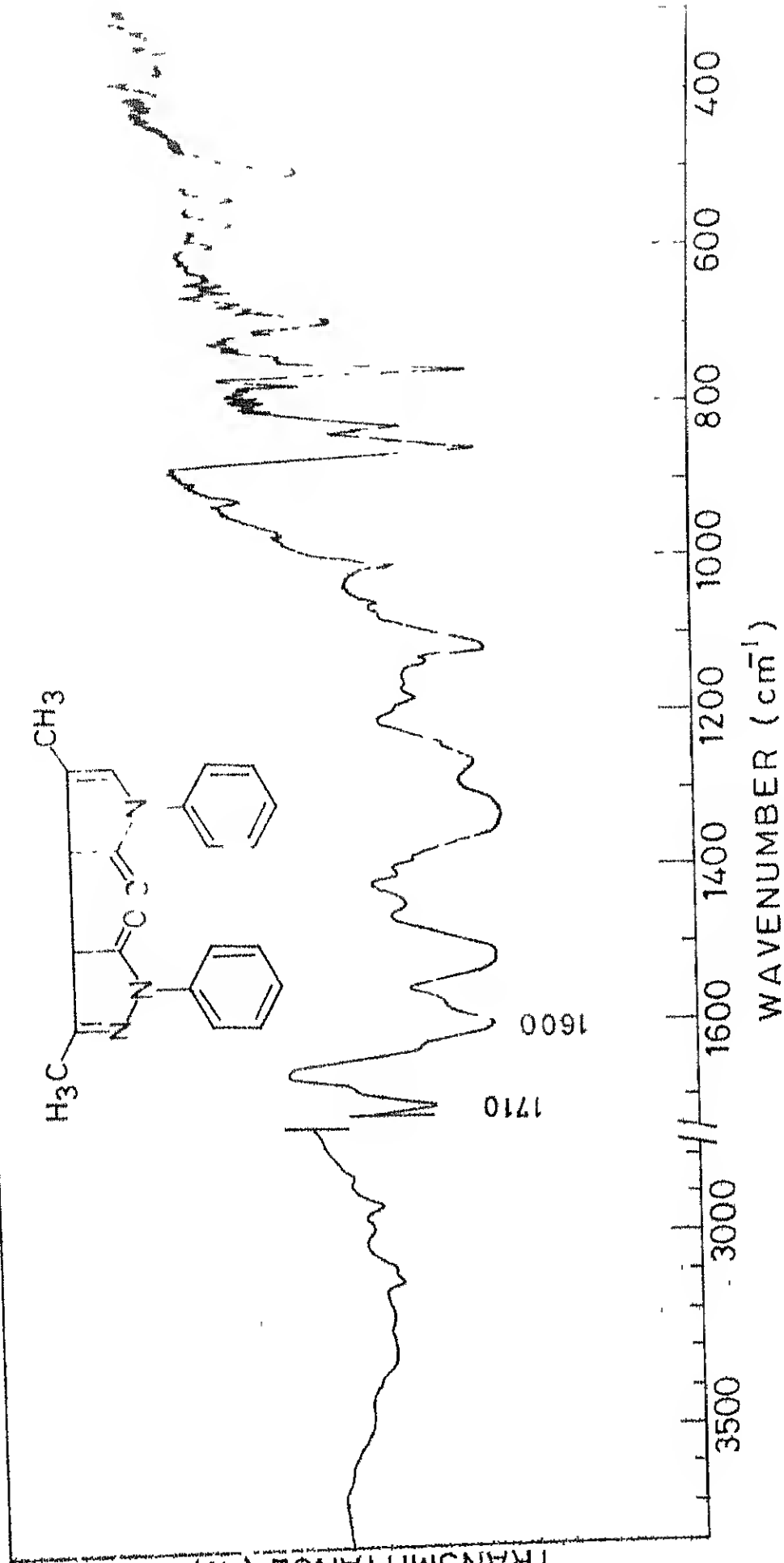


FIG. III.1 IR SPECTRUM OF 143a.

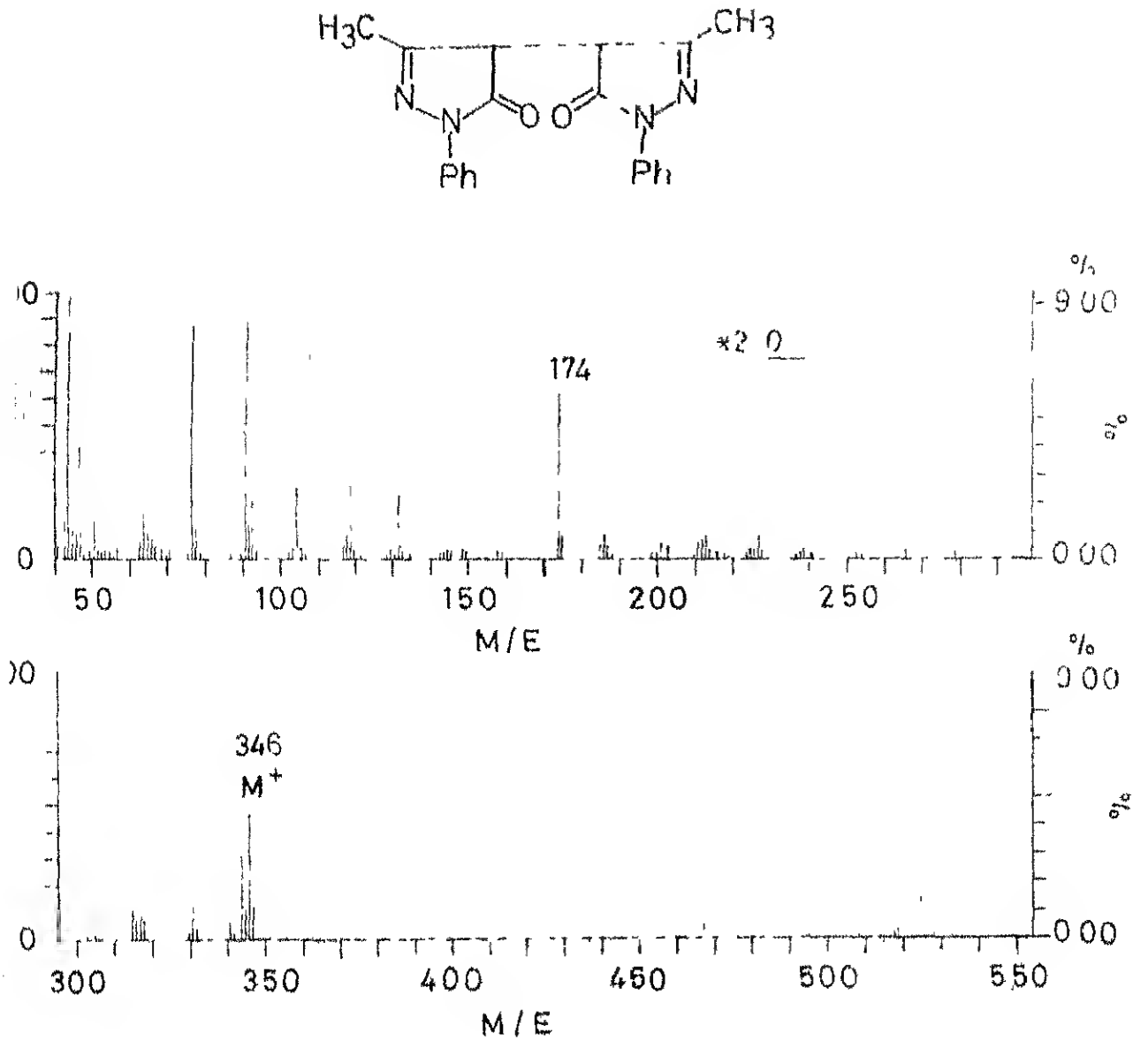


FIG. III.2 MASS SPECTRUM OF 143a

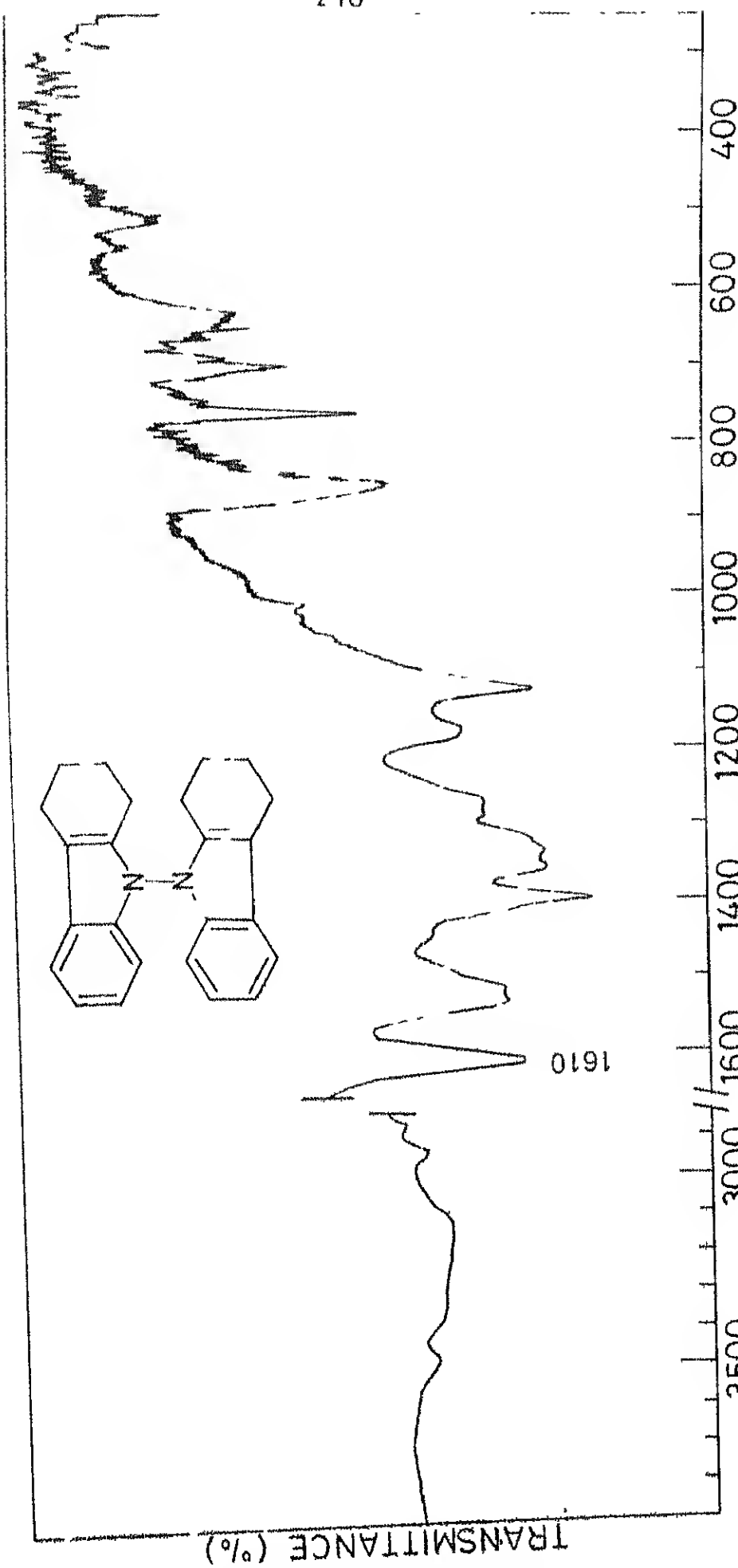


FIG. III.3 IR SPECTRUM OF 146c.

The acids obtained were characterized by the determination of their m.p., TLC behaviour, infra-red analysis and comparing these data with those obtained with the genuine sample of the acid. The oxidative cleavage of aldazines (139a-j) have been effected with CAN in (1:6) molar ratios, in acetonitrile at reflux temperature for 1.5 hr, producing the corresponding aldehydes. These were characterized by the preparation of their 2,4-dinitro-phenyl-hydrazones, and confirmed by comparing these with authentic samples. (cf.Table III,2). At present the mechanism of the reaction is not clear.

The easy conversion of aldehydes to aldazines coupled with their conversion to aldehydes by CAN, makes it an attractive method of protecting an aldehyde group.

Treatment of ceric ammonium nitrate with some heterocycles, such as 1-phenyl-3-methyl-2-pyrazolin-5-one, 141a, 1-[4-nitro-phenyl]-3-methyl-2-pyrazolin-one 141b, 1,2,3,4-tetrahydrocarba-zole took place smoothly at $0^{o}C$ producing their corresponding dimers viz., 4,4'-bis-1-phenyl-3-methyl-2-pyrazolin-5-one 143a, 4,4'-bis-1-[4-nitro-phenyl]-3-methyl-2-pyrazolin-5-one 143b, N,N'-bis-1,2,3,4-tetra-hydrocarbazole 146c respectively. The reaction is believed to proceed via the free radical formation (Scheme III.44-45).

1-[2,4-dinitro-phenyl]-3,5-dimethyl-pyrazole 147d on treatment with CAN produced a hitherto unreported heterocycle.

The mechanism of the formation of this heterocycle is not clear (Scheme III.46).

On the basis of elemental analysis 143a, corresponded to molecular formula $C_{20}H_{18}N_4O_2$. It gave molecular ion peak at 346 in the mass spectrum (Fig. III.2). It exhibited IR absorption bands at 1710($\nu_{C=O}$), 1600($\nu_{C=N}$) (Fig. III.1). The NMR spectrum gave signals at δ 1.9-2.7 (m,6H,CH_3), 7.2-7.4(m, 10H, aromatic), 5.0(s, 2H, CH). It was identified as 4,4'-bis-1-1phenyl-3-methyl-2-pyrazolin-5-one.

On the basis of elemental analysis 143b corresponded to molecular formula, $C_{20}N_{16}N_6O_6$. It gave molecular ion peak at 436 in the mass spectrum. It displayed IR absorption maxima at 1715($\nu_{C=O}$), 1600($\nu_{C=N}$). It gave PMR signals at δ 1.8-2.6(m, 6H, CH_3), 7.1-7.5 (m, 8H, aromatic), 5.1 (s, 2H, CH_2). It was identified as N,N'-bis-1-[4-nitro-phenyl]-3-methyl-2-pyrazolin-5-one(143b).

On the basis of elemental analysis 146c corresponded to molecular formula $C_{24}H_{24}N_2$. It gave molecular ion peak at 340 in the mass spectrum. It exhibited IR absorption band at 1610($\nu_{C=N}$) (Fig. III.3). It gave PMR signals at δ7.8-8.5(m, 8H, aromatic), 2.2-2.4(m, 16H, CH_2). It was identified as N,N'-bis-1,2,3,4-tetrahydro-carbazole.

On the basis of elemental analysis 148d corresponded to molecular formula $C_{11}H_{10}N_4O_6$ (Fig.III.6). Molecular ion peak appeared at 294 in the mass spectrum. It displayed IR absorption maxima at 1620($\nu_{C=N}$) (Fig.III.4). It displayed PMR signals at δ 2.2-2.5 (d, 6H, CH_3), 8.1-9(m, 3H, aromatic), 6.2(s,1H,CH) (Fig.III.5). It was characterized as 148d.

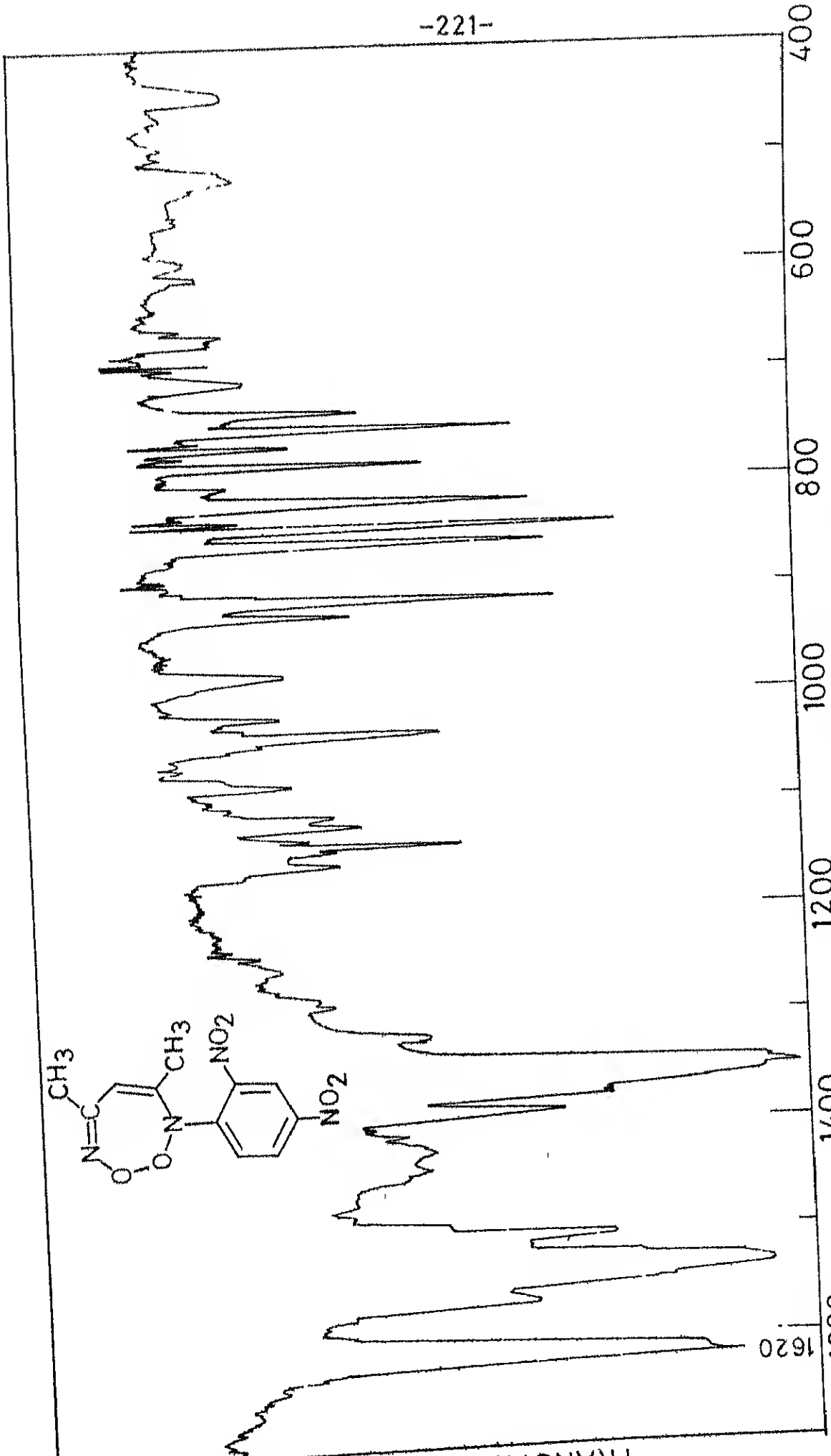


FIG. III.4 IR SPECTRUM OF 148d.

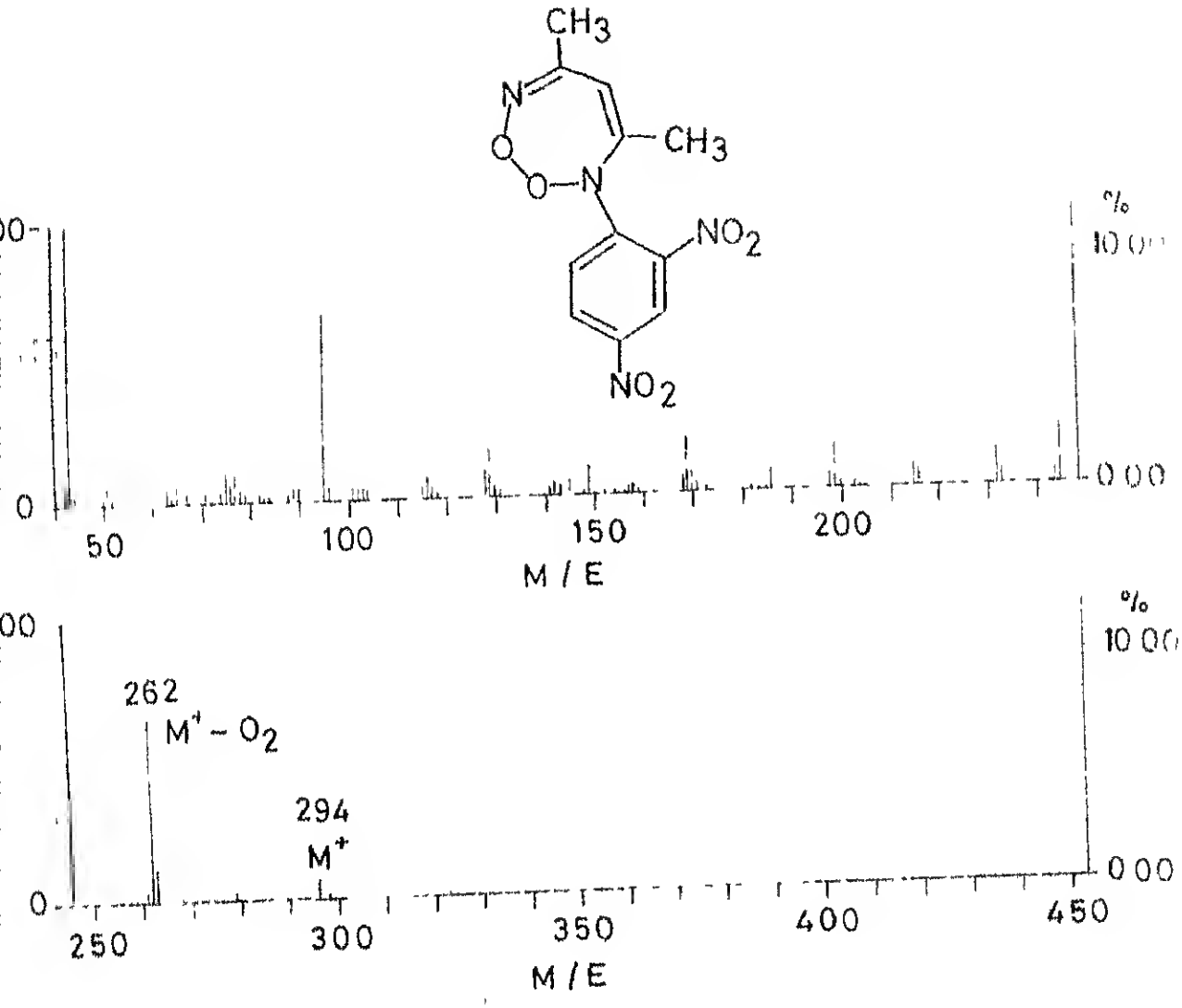
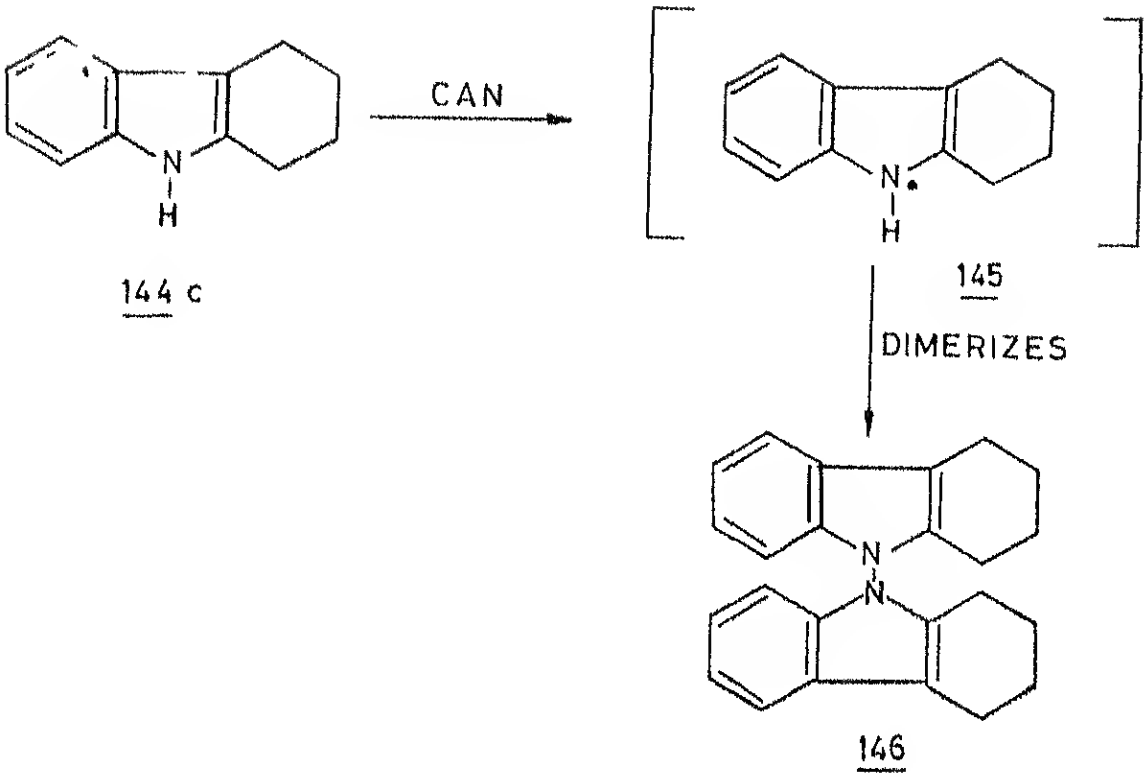


FIG. III.6 MASS SPECTRUM OF 148d

SCHEME III. 43

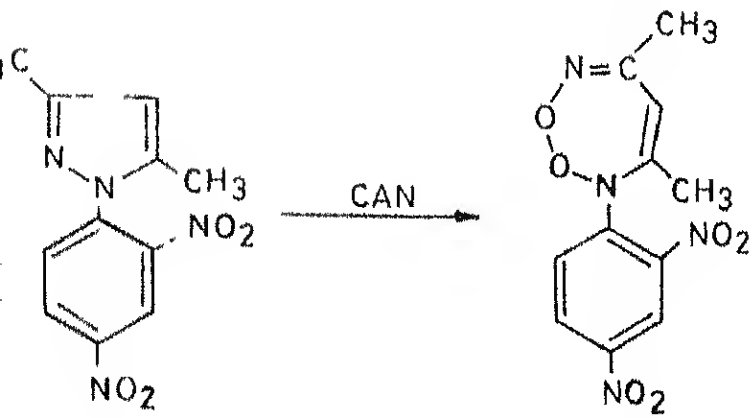


144 c

145

146

SCHEME III. 44



147 d

148

EXPERIMENTAL

All the melting points are uncorrected and were taken on a Fisher-Johns melting point apparatus. The specification of the IR, NMR, and Mass spectrometers were the same as described earlier (*vide* Chapter-I).

Starting materials

A BDH sample of ceric ammonium nitrate was used. The following esters, aldazines and heterocycles (*vide infra*) were prepared according to the methods described elsewhere: ethyl-benzoate, *n*-propyl-benzoate, methyl-benzoate, ethyl-*p*-chloro-benzoate, ethyl-*p*-nitro-benzoate, ethyl-*p*-bromo-benzoate, ethyl-*m*-chloro-benzoate, allyl-benzoate, allyl-*p*-chloro-benzoate, allyl-*m*-chloro-benzoate, allyl-*p*-nitro-benzoate, allyl-*p*-toluate, allyl-*p*-methoxy-benzoate, benzyl-benzoate, benzyl-*p*-chloro-benzoate, benzyl-*m*-chloro-benzoate, benzyl-*p*-toluate, ethyl-phenyl-acetate, *n*-propyl-phenyl-acetate, aldazines (139a-f) (see Table III.2).

1-phenyl-3-methyl-2-pyrazolin-5-one, 1-[*p*-nitro-phenyl]-3-methyl-2-pyrazolin-5-one, 1,2,3,4-tetrahydro-carbazole, 1-[2,4-dinitro-phenyl]-3,5-dimethyl-pyrazole.

OXIDATIVE CLEAVAGE OF ESTERS WITH CERIC AMMONIUM NITRATE

General procedure:

To a stirred solution of ester (1 mmol) in aqueous-acetonitrile (1:4, 5 ml) was added a solution of ceric ammonium nitrate (4 mmol) in acetonitrile. The resulting solution was refluxed for 5-6 hr at 80°, followed by cooling to room temperature. The reaction mixture was diluted with water (10 ml) and extracted with ether (3x5 ml). The ethereal layer was separated and extracted with sodium bicarbonate solution (5%). The aqueous layer was acidified (dil. HCl) and shaken up with ether (3x5 ml). The acid component, dissolved in ether, was dried over Na_2SO_4. Ether was distilled off to recover the acid, which was characterized by the determination of its m.p., TLC behaviour, infrared, analysis, and comparing these data with those obtained with the genuine sample of the acid. The yields, m.p. of the corresponding acids are listed in the Table III.1.

OXIDATIVE CLEAVAGE OF ALDAZINES (139a-j)

General procedure:

To a stirred solution of aldazine (0.001 mol) maintained at 80° in acetonitrile (6 ml) was added CAN (0.006 mol) in acetonitrile (6 ml). The reaction mixture was refluxed for 1.5 hr. As soon as the reaction was complete (TLC monitoring), reaction mixture was cooled to room temperature, and diluted with water,

followed by extraction with ether (2x10 ml). The ethereal layer was washed with water and dried (Na_2SO_4). On evaporating off the solvent, the residual material was reacted with an alcoholic solution of 2,4-dinitrophenylhydrazine (in acidic medium). The resulting 2,4-dinitrophenylhydrazone was collected by filtration and identified by comparison with authentic samples. The yields, m.p. of the corresponding 2,4-dinitrophenylhydrazones are listed in Table III.2).

PREPARATION OF THE DIMERS OF SUBSTITUTED 2-PYRAZOLIN-5-ONE(143a-b) AND TETRAHYDROCARBAZOLE(146c)

General procedure:

To a stirred solution of 141a (0.001 mol) in acetonitrile (6 ml) was added (0.0025 mol) CAN (0.01 mol) in acetonitrile (6 ml) at 0°. As soon as the reaction was complete (TLC monitoring), reaction mixture was diluted with water, followed by extraction with ether (2x10 ml). The ethereal layer was washed with water and dried (Na_2SO_4). On evaporating off the solvent, the residual material obtained was crystallized with ethanol, producing 143a. Compounds 143b and 146c are obtainable from the appropriate reactants under reaction condition described above.

Note: When 1-[2,4-dinitrophenyl]-3,5-dimethyl pyrazole is treated in the manner outlined above - a new heterocyclic system (148d) is obtained.

4,4'-bis-1-phenyl-3-methyl-2-pyrazolin-5-one:

Yield: 0.519g, (60%), m.p. 278-279° (lit. 290°, dec).

Anal for $C_{20}H_{18}N_4O_2$: Calcd, C, 69.36; H, 5.20; N, 16.18%
Found, C, 68.16; H, 6.21; N, 17.56%

IR Spectrum(KBr), ν_{max}: 1710($\nu_{C=O}$), 1600($\nu_{C=N}$), 1380, 1000, 840 cm^{-1}.

PMR Spectrum($DMSOd_6$), δ ppm: 1.9-2.7(m, 6H, CH_3), 7.2-7.4(m, 10H, aromatic), 5.0 (s, 2H, CH).

Mass spectrum, m/e: 346(M^+), 174.

4,4'-bis-[4-nitrophenyl]-3-methyl-2-pyrazolin-5-one:

Yield: 0.676g, (62%), m.p. 250-252° (lit. 255°, dec).

Anal for $C_{20}H_{16}N_6O_6$: Calcd, C, 55.04; H, 3.66; N, 19.26%
Found, C, 54.68; H, 4.21; N, 20.15%

IR Spectrum(KBr), ν_{max}: 1715($\nu_{C=O}$), 1600($\nu_{C=N}$), 1370, 1100, 830 cm^{-1}.

PMR Spectrum ($DMSOd_6$), δ ppm: 1.8-2.6(m, 6H, CH_3), 7.1-7.5(m, 8H, aromatic), 5.1(s, 2H, CH).

Mass spectrum, m/e: 436(M^+).

N,N'-bis-1,2,3,4-tetrahydro-carbazole:

Yield: 0.501g, (59%), m.p. 260°(dec).

Anal for $C_{24}H_{24}N_2$: Calcd, C, 84.70; H, 7.05; N, 8.23%
Found, C, 85.61; H, 7.86; N, 9.15%

IR Spectrum(KBr), ν_{max}: 1610($\nu_{C=N}$), 1400, 1130, 850, 710 cm^{-1}.

PMR Spectrum($DMSOd_6$), δ ppm: 7.8–8.5(m, 8H, aromatic), 2.2–2.4(m, 16H, CH_2).

Mass spectrum, m/e: 340(M^+).

Compound 148d:

Yield: 0.448g, (61%), m.p. 107–108°.

Anal for. $C_{11}H_{10}N_4O_6$: Calcd, C, 44.89; H, 3.40; N, 19.04
Found, C, 44.75; H, 3.30; N, 19.01%

IR Spectrum(KBr), ν_{max}: 1620($\nu_{C=N}$), 1350, 1140, 840, 750 cm^{-1}.

PMR Spectrum($DMSOd_6$), δ ppm: 2.2–2.5(d, 6H, CH_3), 8.1–9(m, 3H, aromatic), 6.2(s, 1H, CH).

Mass spectrum, m/e: 294(M^+), 262.

TABLE-III.1

CERIC AMMONIUM NITRATE OXIDATION OF ESTERS

$$R^1-\overset{\overset{O}{\|}}{C}-OR^2$$

Product	R^1	R^2	M.P./ (lit.) ^oC	Yield(%)
138a	C_6H_5	CH_3	122-123 (122-123)	56
138b	C_6H_5	C_2H_5	122-123 (122-123)	59
138c	C_6H_5	$n-C_3H_7$	120-122 (122-123)	61
138d	$p-ClC_6H_4$	C_2H_5	238-240 (239-241)	58
138l	$m-ClC_6H_4$	C_2H_5	154-156 (155-157)	58
138f	$p-NO_2C_6H_4$	C_2H_5	239-240 (239-241)	62
138g	$p-BrC_6H_4$	C_2H_5	251-253 (252-254)	65
138h	C_6H_5	$CH_2-CH=CH_2$	121-123 (121-123)	78
138i	$p-ClC_6H_4$	$CH_2-CH=CH_2$	239-240 (239-241)	74
138j	$m-ClC_6H_4$	$CH_2-CH=CH_2$	155-156 (155-157)	70
138k	$p-NO_2C_6H_4$	$CH_2-CH=CH_2$	238-240 (239-241)	70
138l	$p-CH_3C_6H_4$	$CH_2-CH=CH_2$	179-181 (180-182)	69
138m	$p-OCH_3C_6H_4$	$CH_2-CH=CH_2$	181-185 (182-185)	85

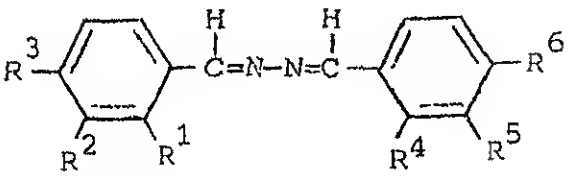
Table(contd.)..

Table(contd.)..

138n	C_6H_5	$CH_2C_6H_5$	121–123 (122–123)	64
138o	p-ClC_6H_4	$CH_2C_6H_5$	239–240 (239–241)	65
138p	p-$CH_3C_6H_4$	$CH_2C_6H_5$	181–182 (180–182)	70
138q	$C_6H_5CH_2$	C_2H_5	76–77 (77)	68
138r	$C_6H_5CH_2$	n-C_3H_7	75–77 (77)	65

TABLE-III.2

Oxidative cleavage of aldazines with CAN



Product	Substituents						M.P.(lit.) (°C)	Yield (%)
	R^1	R^2	R^3	R^4	R^5	R^6		
140a	H	H	H	H	H	H	236-237 (237)	82
140b	H	H	Cl	H	H	Cl	264-265 (265)	79
140c	H	H	Br	H	H	Br	264-265 (265)	81
140d	H	H	OCH_3	H	H	OCH_3	253-254 (254)	76
140e	H	OCH_3	OCH_3	H	OCH_3	OCH_3	263-264 (264)	75
140f	H	H	NO_2	H	H	NO_2	319-320 (320)	72
140g	NO_2	H	H	NO_2	H	H	264-265 (265)	70
140h	H	NO_2	H	H	NO_2	H	290-292 (292)	80
140i	H	Cl	H	H	Cl	H	247-248 (248)	74
140j	Cl	H	H	Cl	H	H	207-209 (209)	73

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CHAPTER-IV

PHOTOLYTIC STUDIES ON SOME SUBSTITUTED CHALCONES

IV.1 ABSTRACT

Photochemical irradiation of some substituted chalcones, viz., 4'-chloro-chalcone, 3,4-dimethoxy-4'-chloro-chalcone, 4'-chloro-4-acetamido-chalcone has been studied in different solvents such as benzene, acetone, methanol, ethanol, acetic acid, employing the molecular oxygen. Srinivasan Griffin Rayonet Photochemical reactor, equipped with 2537A^{o} light source, was used for carrying out the photochemical irradiations.

Irradiation of 4'-chloro-chalcone, 3,4-dimethoxy-4'-chloro-chalcone in acetone/molecular O_2 for 46 hr gave rise to their corresponding indenones.

4'-chloro-chalcone, 3,4-dimethyoxy-4'-chloro-chalcone, in benzene/molecular O_2 were photochemically irradiated for 44 hr, leading to the formation corresponding of flavanones.

4'-chlorochalcone, 3,4-dimethoxy-4'-chloro-chalcone on irradiation in methanol/molecular O_2 for 42 hr produced p-chlorobenzoic acid.

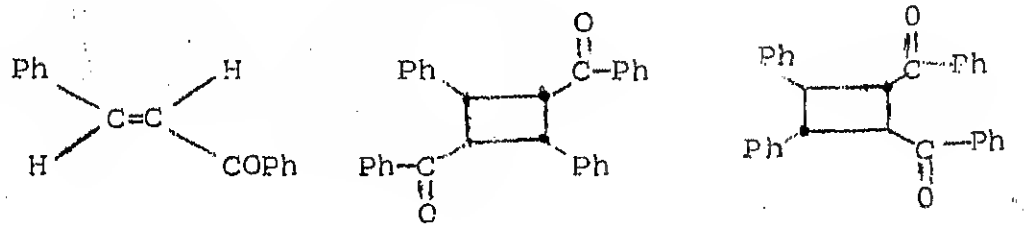
IV.2 Introduction[32]

Photoisomerization of trans chalcone[1], trans-2-hydroxy-chalcone[2] and other substituted chalcones[3,4] and heterocyclic analogues of chalcones[5] into their corresponding cis isomers has been described in the literature. Thus, cis-2-methoxy-chalcone is convertible to cis-2-hydroxy-chalcone (photochemical demethylation)[2] by prolonged irradiation with sunlight. Some chalcones, on the other hand, have a great tendency to undergo resinification[6] when irradiated either in the solid state or solution, viz., 4,4'-dimethyl (and 4,4'-dimethoxy) chalcones. The solid state photochemistry of some 2'-nitro-chalcones has been studied.[7] Various parameters seem to govern the specific pathway followed by the photochemical reaction, for example, molecular conformation and its retention and the molecular packings.

Several chalcones have been reported to undergo photochemical dimerizations, viz., chalcone,[6,8] 4'-methyl-chalcone,[6] 4-methoxy-chalcone[10], and the thiophene analogue[11] of chalcone. The cyclobutane type of structure[6,8] has been assigned to chalcone dimers.[9-10]

The high melting (m.p. 226°) isomer, (produced by solid state irradiation) has been assigned a structure 2, while the low melting (m.p. 126°) isomer, produced in solution, has been assigned a structure 3 (vide infra).

Scheme IV.1

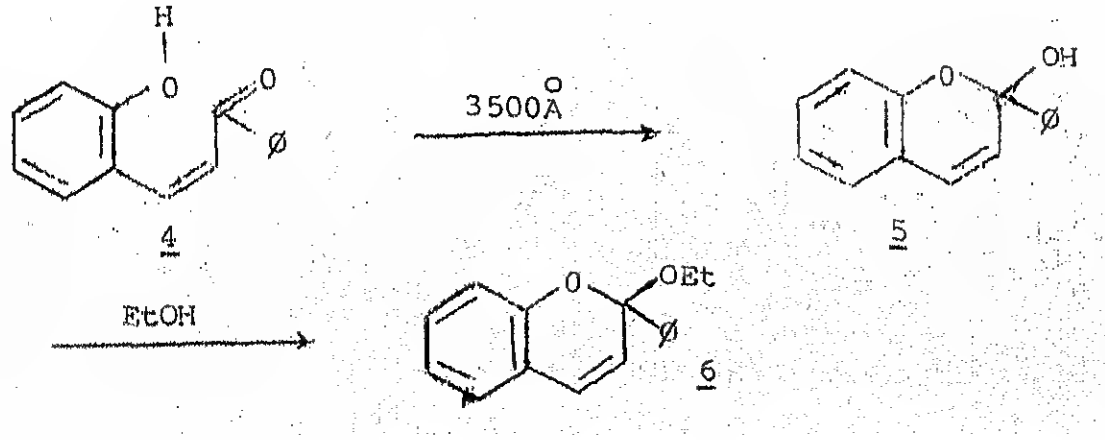


1 2 3

Dimerization of chalcone and 4-methoxy-chalcone[13] do not take place if these are irradiated in presence of Uranyl-chloride[12].

Photoinduced dimerization of 4-methoxy-chalcone is reported[13-15] to take place with the aid of 9,10-dihydro-anthracene. Photolysis of 2-o-hydroxy chalcone in ethanol is reported[16] to yield 2-ethoxy-flav-3-ene (96%) and a very small amount of (1%) flavene, (Scheme IV.2).

Scheme IV.2



4 5 6

4'-chlorochalcone, 3,4-dimethoxy-4'-chloro-chalcone on irradiation in methanol/molecular O_2 for 42 hr produced p-chlorobenzoic acid.

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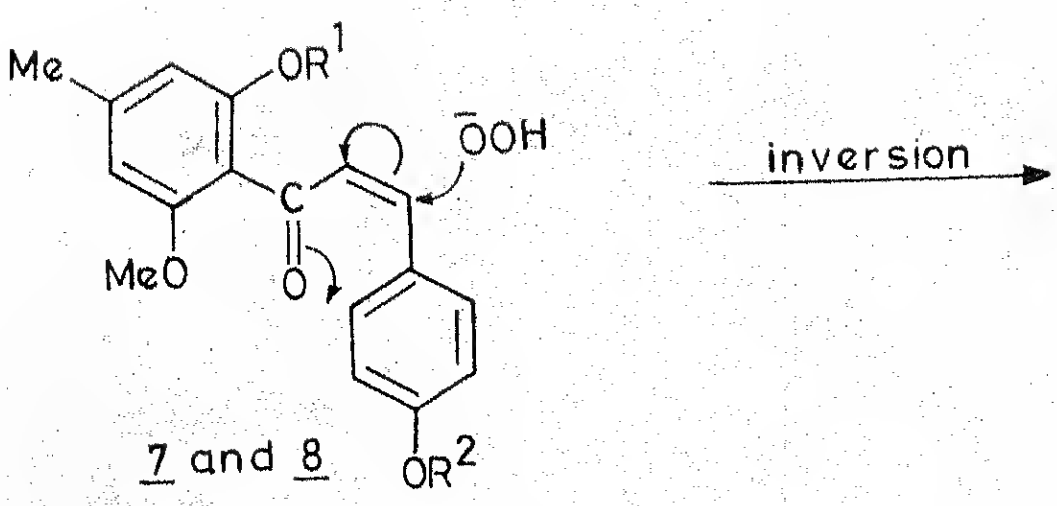
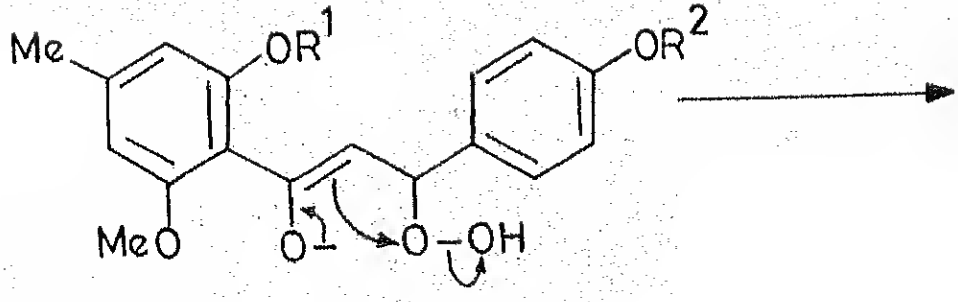
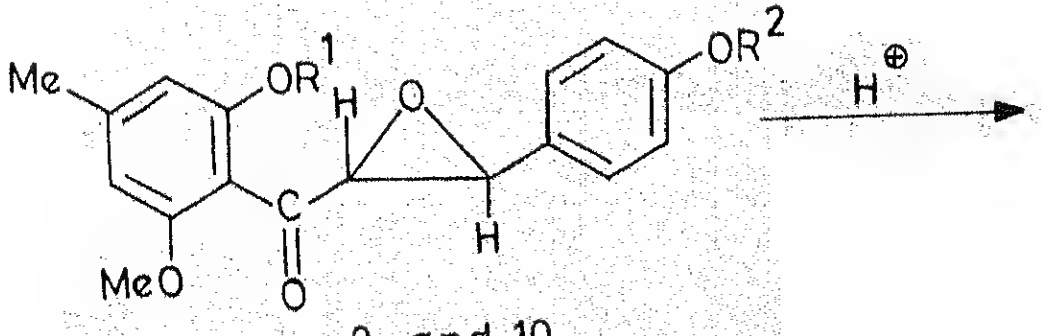
Several chalcones have been reported to undergo photochemical dimerizations, viz., chalcone,[6,8] 4'-methyl-chalcone,[6] 4-methoxy-chalcone[10], and the thiophene analogue[11] of chalcone. The cyclobutane type of structure[6,8] has been assigned to chalcone dimers.[9-10]

Scheme IV.3



7 and 8





9 and 10

9, $R^1 = CH_2OMe$, $R^2 = Me$

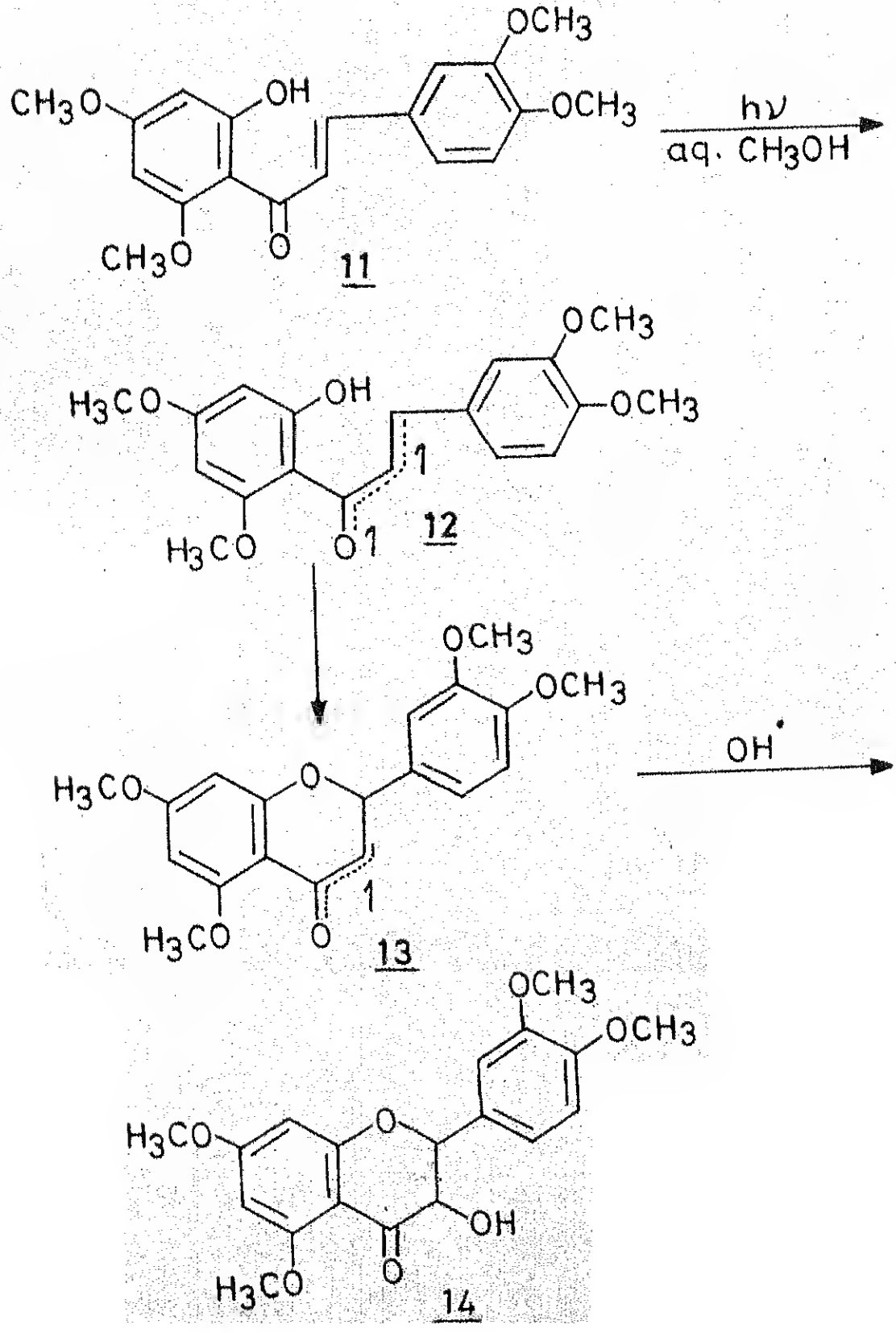
10, $R^1 = Me$, $R^2 = CH_2OMe$

Methylene blue-sensitized photochemical oxidation by visible light has been described[17] in the case of 2'-hydroxy-4',6',3,4-tetramethoxy chalcone, leading to the formation of 5,7,3',4'-tetramethoxy flavanonol. The 3-hydroxylic function in the flavanonol is assumed to a rise from the hydroxylic radical generated by the photolysis of aqueous methanol, used as the solvent.

Photoisomerization[3] of trans chalcone, trans-2-hydroxy chalcone and other substituted chalcones and heterocyclic analogues of chalcones in to their corresponding cis-isomer has been described in the literature. In alkaline peroxide the fully o-substituted pairs of trans and cis-chalcones 7 and 8 form trans epoxide 9 and 10 which could be stored unchanged for at least 6 months (Scheme IV.3).

Chalcones are the important key intermediates for the biogenesis[17] of naturally occurring oxygen heterocycles, particularly the flavonoids. They can be conveniently converted to the flavonoids of different oxygenation levels by chemical as well as enzymatic methods. Using chalcone precursors, Pelter et al. have shown that flavanonols are generated from chalcones in plants. The radical nature of the reaction was confirmed by its inhibition on addition of quinol, a radical quencher. The radical 12 undergoes an intramolecular radical abstraction from 2'-hydroxyl group to produce 13 which yields the flavanonol either by radical-water

Scheme IV.4


OCH3
CH3O
OH
OCH3
hν
aq. CH3OH
CH3O
O
11
OCH3
H3CO
OH
OCH3
1
H3CO
O1
12
OCH3
OCH3
OH·
H3CO
O
1
H3CO
O
13
OCH3
OCH3
H3CO
O
OH
H3CO
O
14

molecule collision or by combination with the hydroxyl radical formed by the photolysis of aqueous methanol (Scheme IV.4).

Photolysis of chalcone derivatives

Irradiation of trans-chalcone oxide[18-20] (15) in acetonitrile with 313 nm radiation led to the formation of dibenzoyl methane as the major product (Scheme IV.5).

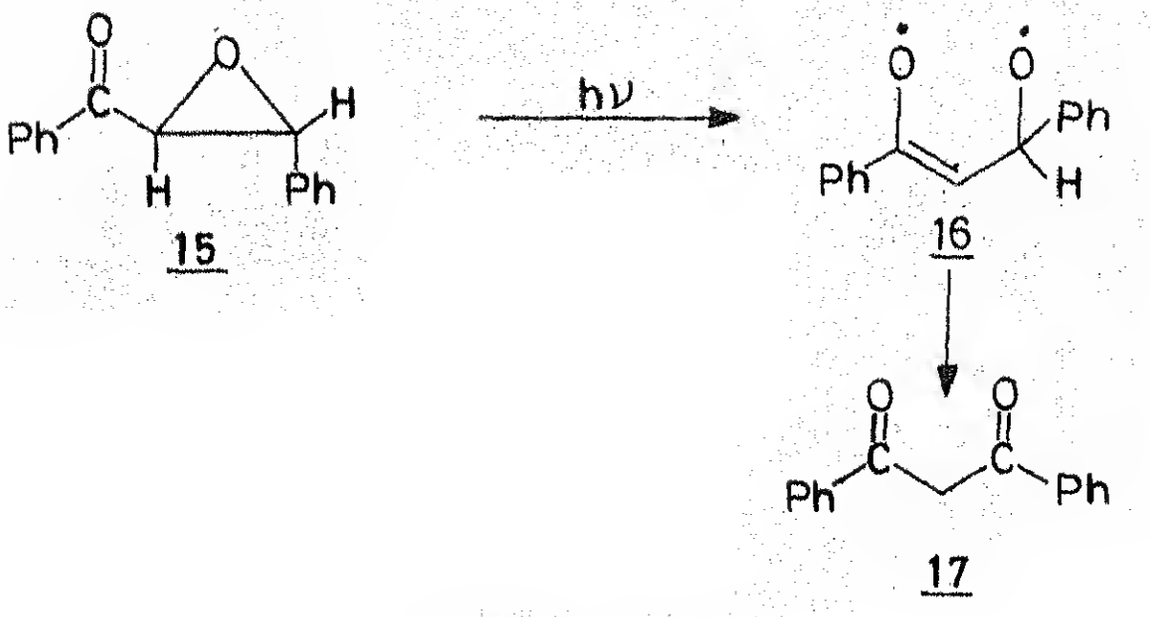
However, irradiation of chalcone epoxide (15) in presence of a six fold excess of methyl acrylate, an efficient dipolarophile, led to the formation of substituted tetrahydrofuran adduct in addition to dibenzoyl-methane (Scheme IV.6).

Chalcone epoxides are reported to undergo photooxidative cleavage, yielding a mixture of acid and aldehyde.[18] An illustrative example is the photochemical transformation, 2',3,4,4'-tetramethoxy-chalcone epoxide[18] to veratraldehyde and 2,4-dimethoxybenzoic acid. Some of the chalcone-semi-carbazones are reported to exhibit photochemical isomerism.[21] Example are: p-methyl-chalcone and p-methoxy-p'-methyl-chalcone[21].

Miscellaneous photochemical reactions

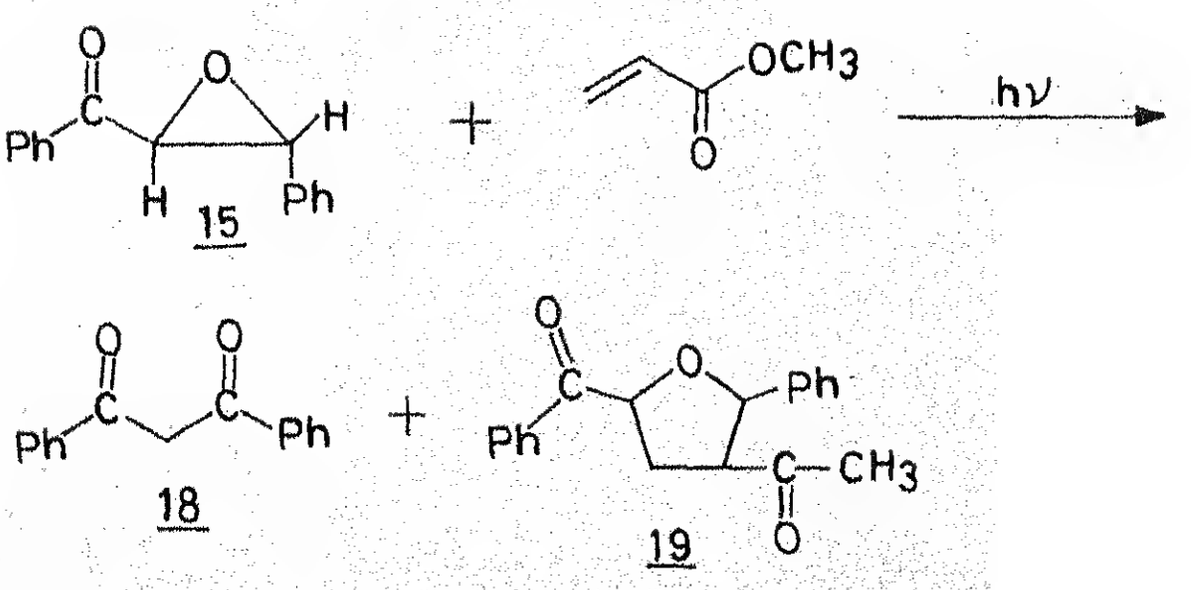
Oxidative photocoupling[23-23] reactions have been investigated for the cyclization of cis and trans stilbene and their derivatives to form substituted phenanthrenes. Para-fluro, chloro-and bromo-stilbenes photocyclize in yield of 60-85% (Scheme IV.7).

Scheme IV.5



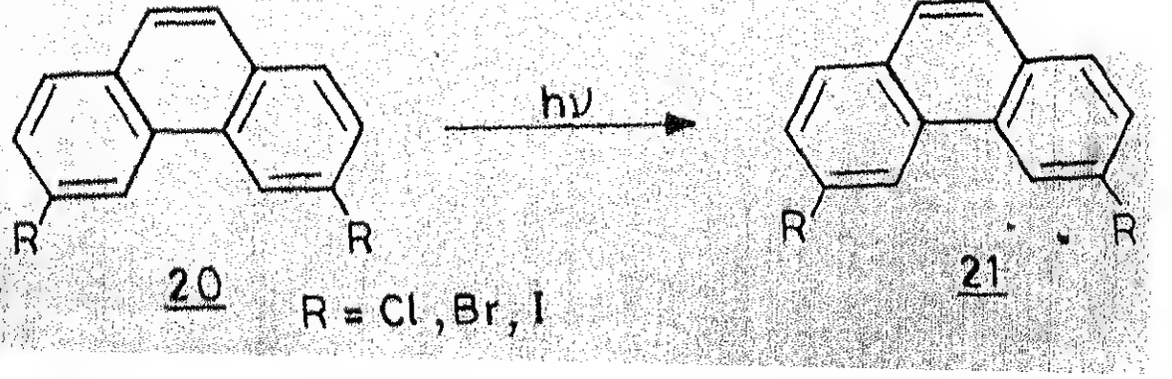
15 16 17

Scheme IV.6



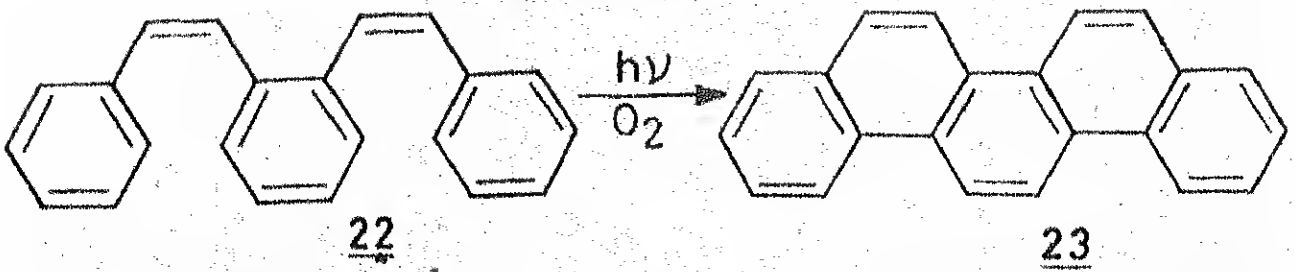
15 18 19

Scheme IV.7

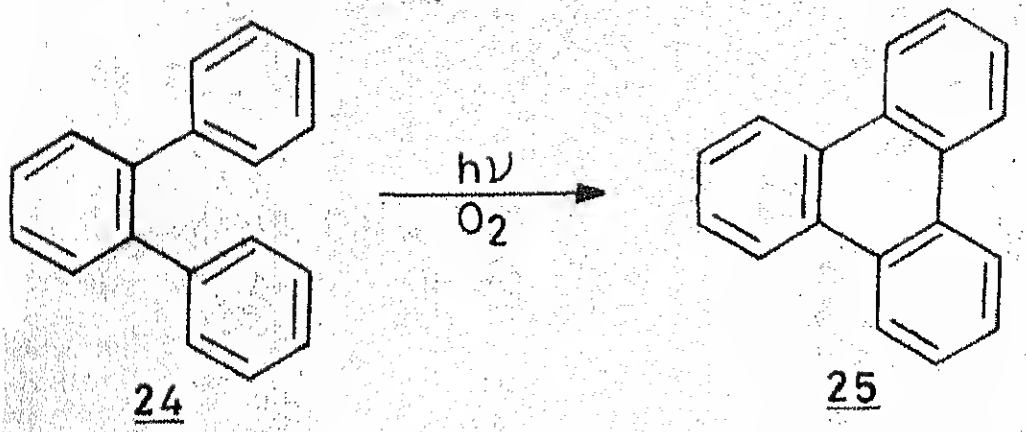


20 R = Cl, Br, I 21

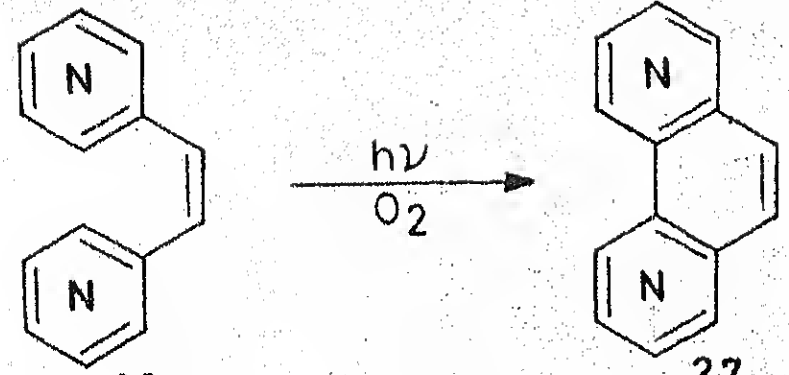
Scheme IV.8



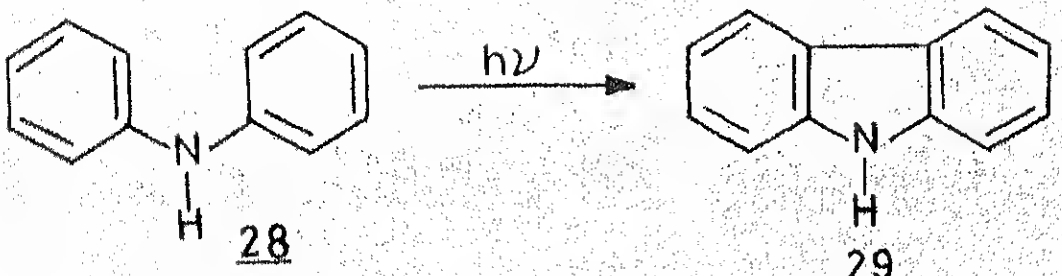
22 23



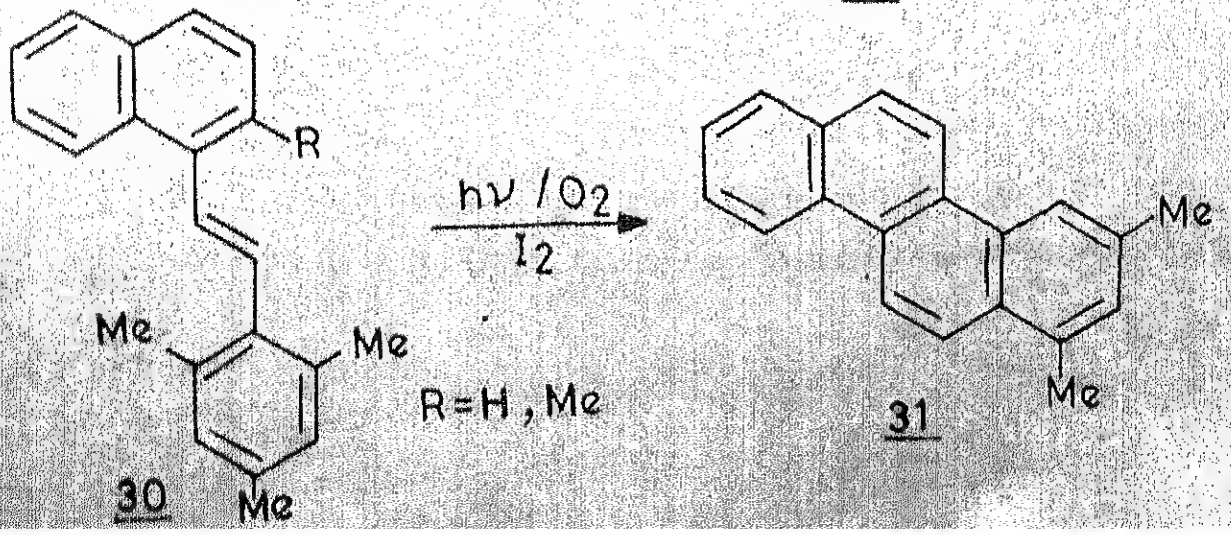
24 25



26 27



28 29



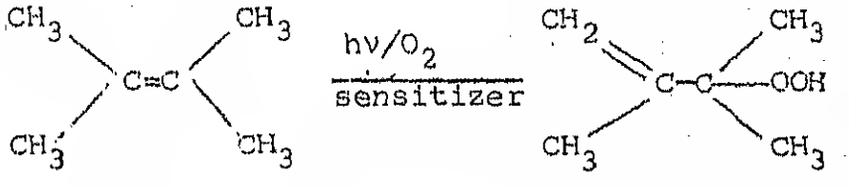
30 31

The synthesis of a large number of polycyclic and poly-heterocyclic aromatics has been achieved by oxidative photo coupling reactions. The synthesis of picene from 1,2-distyryl benzene, triphenylene from ortho-terphenyl, phenanthroline from 1,2-dipyridyl ethylenes, has been accomplished by this method (Scheme IV.8).

A solution of isophorone[26-27], in aqueous acetic acid, is irradiated under a gentle nitrogen sparge for 20 hr, giving rise to isophorone dimer, (Scheme IV.9).

Irradiation of 2-phenyl-3-[2-pyridyl]acrylonitrile[30] in benzene produced benzo [7]quinoline-6-carbonitrile (Scheme IV.10). 2,3-dimethyl-2-butene on irradiation[28] gave rise to 3-hydroperoxy-2,3-dimethyl-1-butene.

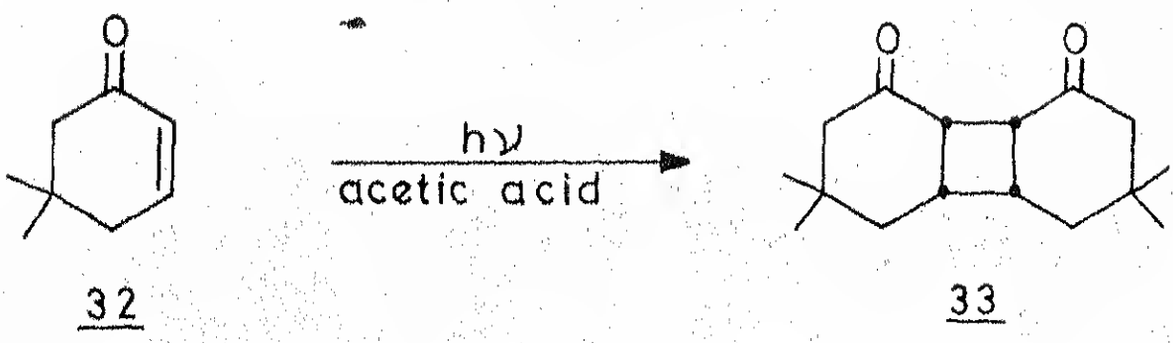
Scheme IV.11



36 37

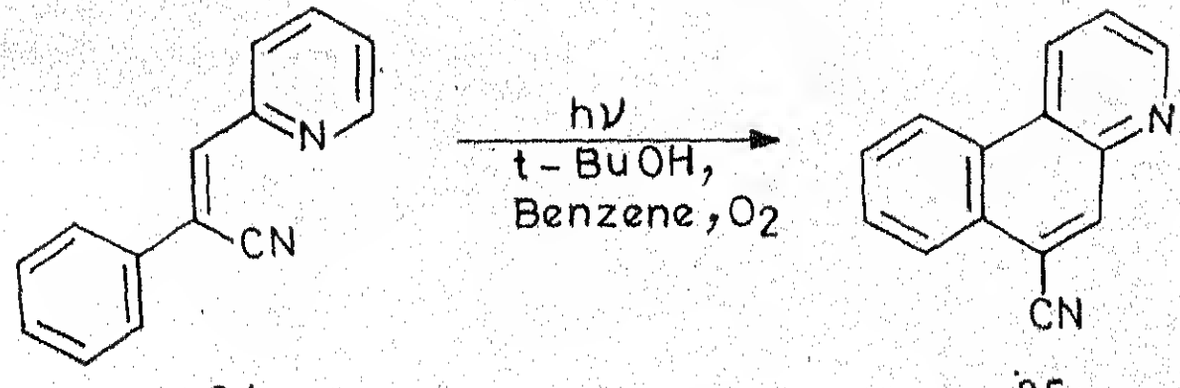
Irradiation of aerated solutions of 1,2,3,4,4a,9a, hexahydro-fluorene in absolute methanol in the presence of sulphuric acid, is reported[25] to give 1,2,3,4,4a,9a-hexahydro-4a-methoxy-xanthene (Scheme IV.12).

Scheme IV.9



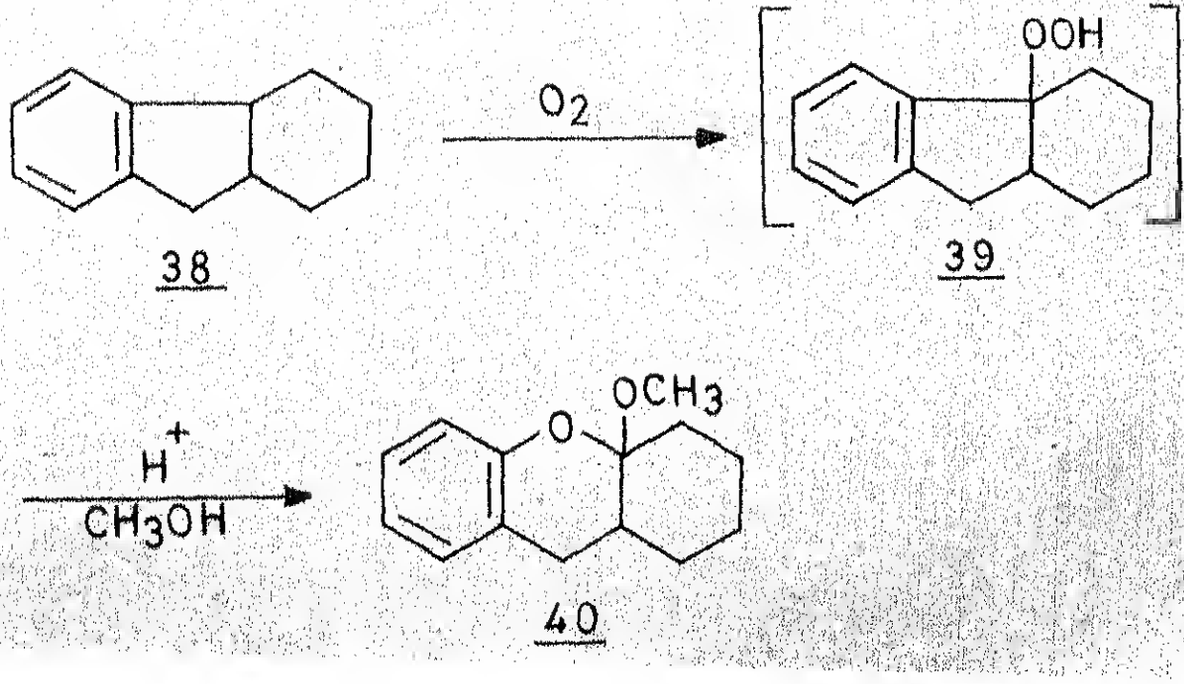
32 33

Scheme IV.10



34 35

Scheme IV.12



38 39 40

Photochemical irradiation of 2,5-dimethyl-furan furnished 5-hydroperoxy-2,5-dimethyl dihydro-furan[29] (Scheme IV.13). Irradiation[30] of bi-1-cyclohexen-1-yl in presence of erythrosin B as a sensitizer, produced a stable epidioxide in 51% yield (Scheme IV.14).

IV.3 RESULTS AND DISCUSSION

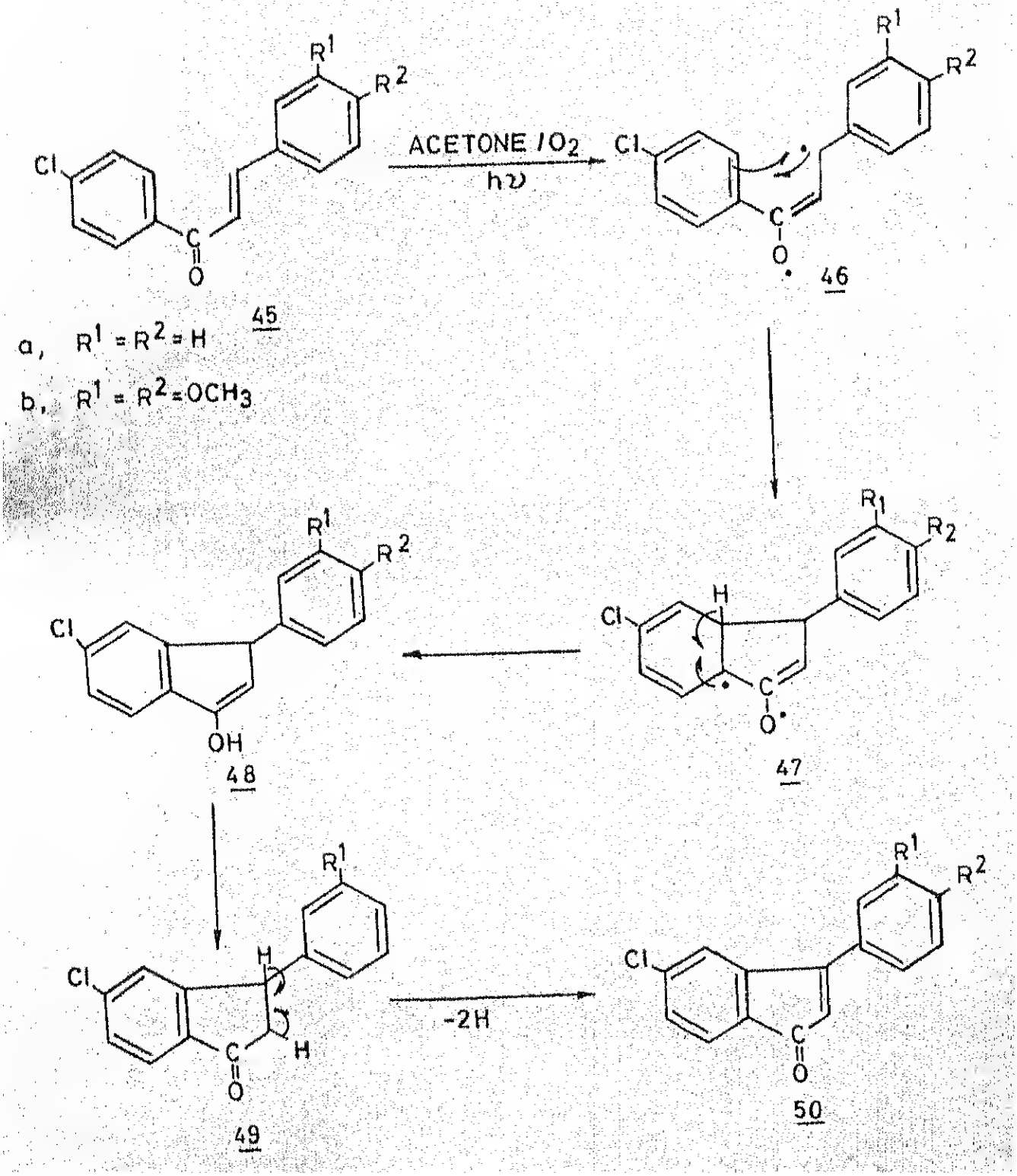
Photochemical irradiation of 4'-chloro-chalcone, 3,4-dimethoxy-4'-chloro-chalcone, 4'-chloro-4-acetamido-chalcone has been studied in different solvents, viz., benzene, acetone, methanol, ethanol, acetic acid using molecular oxygen.

Photochemical irradiation of 4'-chloro-chalcone, 3,4-dimethoxy-4'-chloro-chalcone in acetone-molecular oxygen for 46 hr produced their corresponding indenones (50a-b) (Scheme IV.15). Irradiation of 4'-chloro-chalcone, 3,4-dimethoxy-4'-chloro-chalcone in benzene molecular oxygen for 44 hr gave rise to their corresponding flavanones (53a-b) (Scheme IV.16).

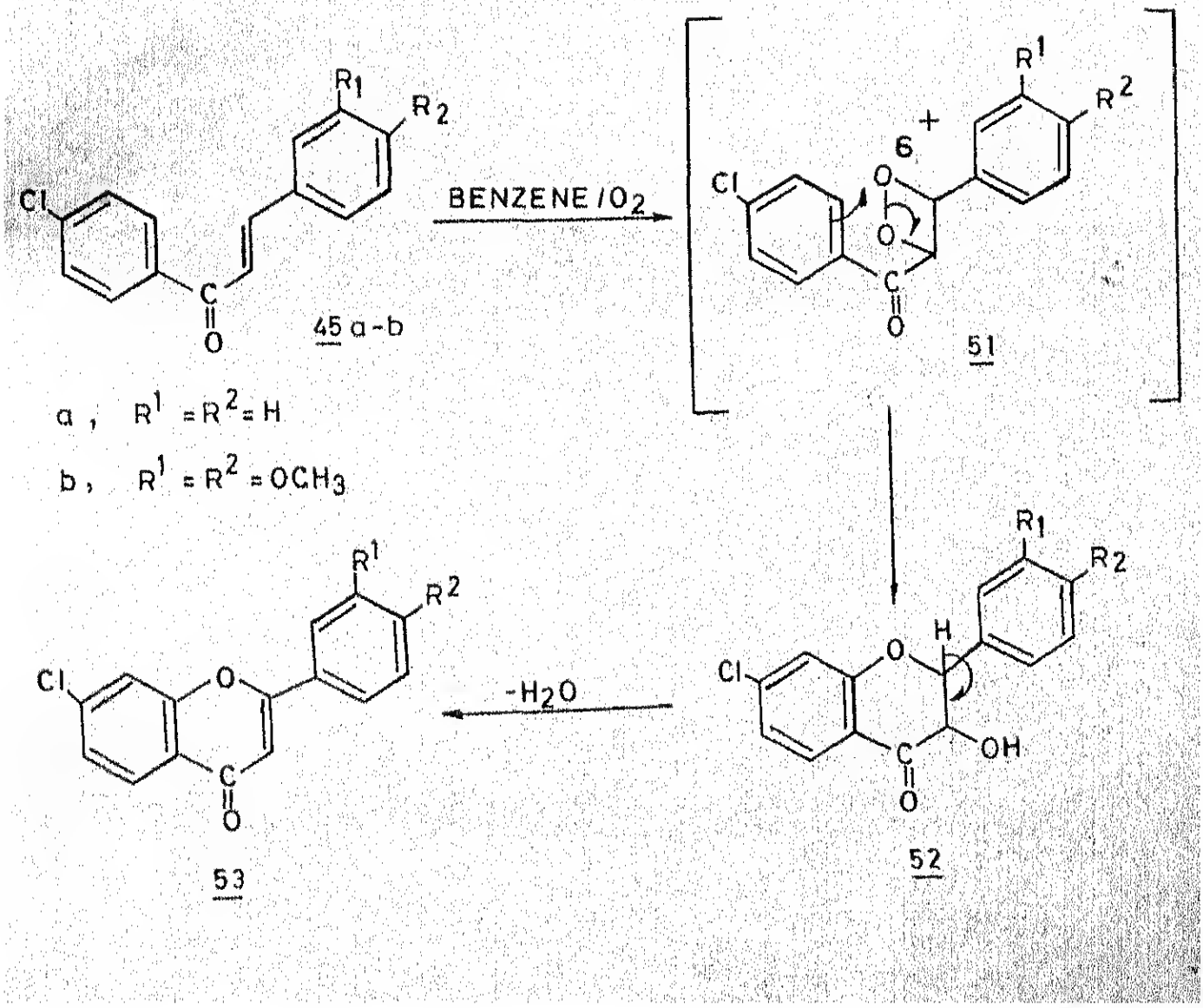
Irradiation of 4'-chloro-chalcone, and 3,4-dimethoxy-4'-chloro-chalcone in methanol molecular oxygen for 42 hr produced p-chloro benzoic acid (59a-b) (Scheme IV.17).

4'-chloro-chalcone, 3,4-dimethoxy-4'-chloro-chalcone on irradiation, in ethanol, acetic acid oxygen did not yield any product, even after prolonged irradiation. Likewise, 4'-chloro-4-acetamido-chalcone on irradiation in benzene, acetone, methanol,

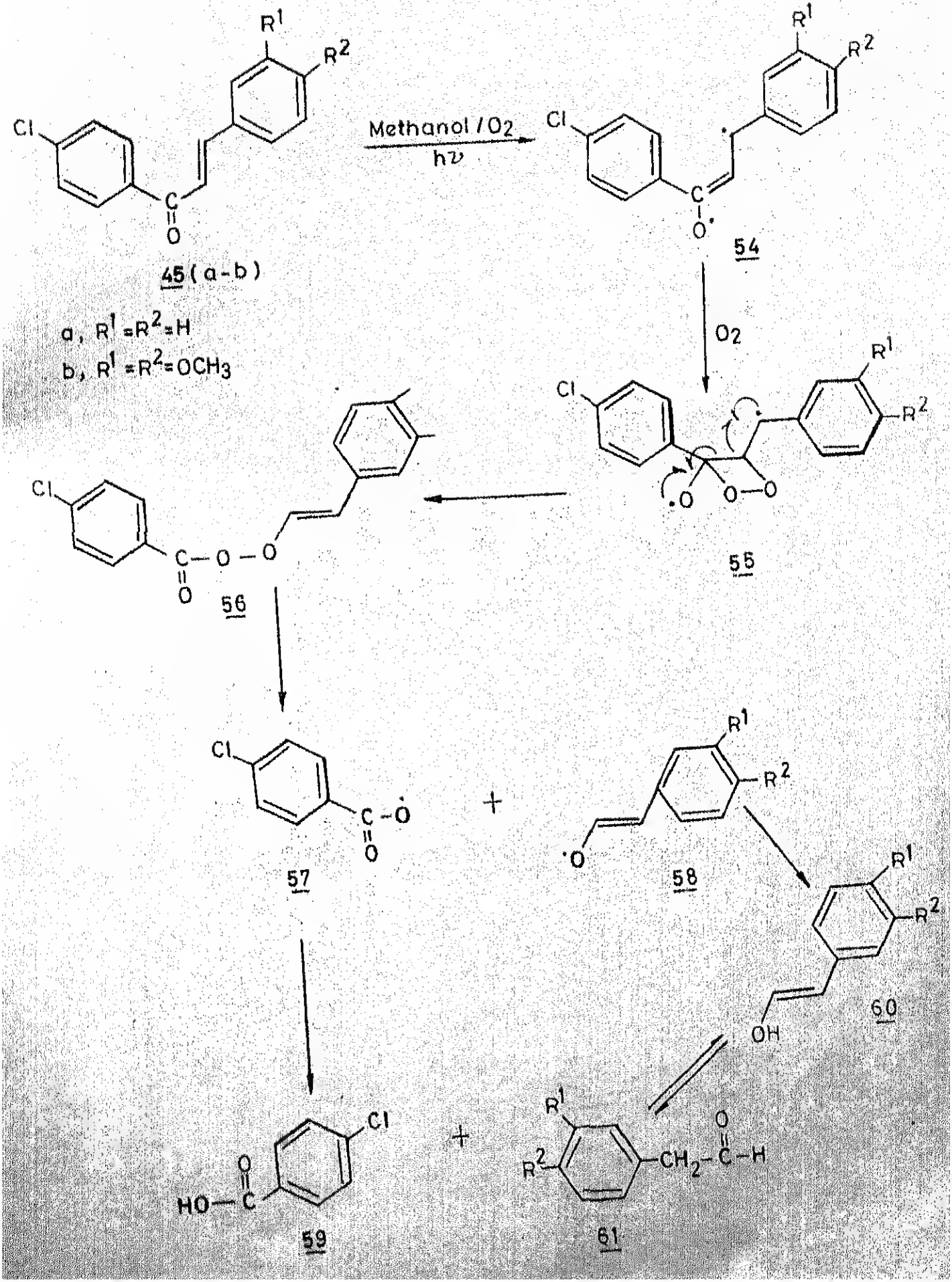
SCHEME IV.15



SCHEME IV. 16


R1
R2
Cl
C
O
45 a-b
BENZENE/O2
R1
R2
+
δ
O
Cl
O
C
O
51
a , R1 = R2 = H
b , R1 = R2 = OCH3
R1
R2
Cl
O
C
O
53
-H2O
R1
R2
H
Cl
O
OH
C
O
52

SCHEME IV.17.



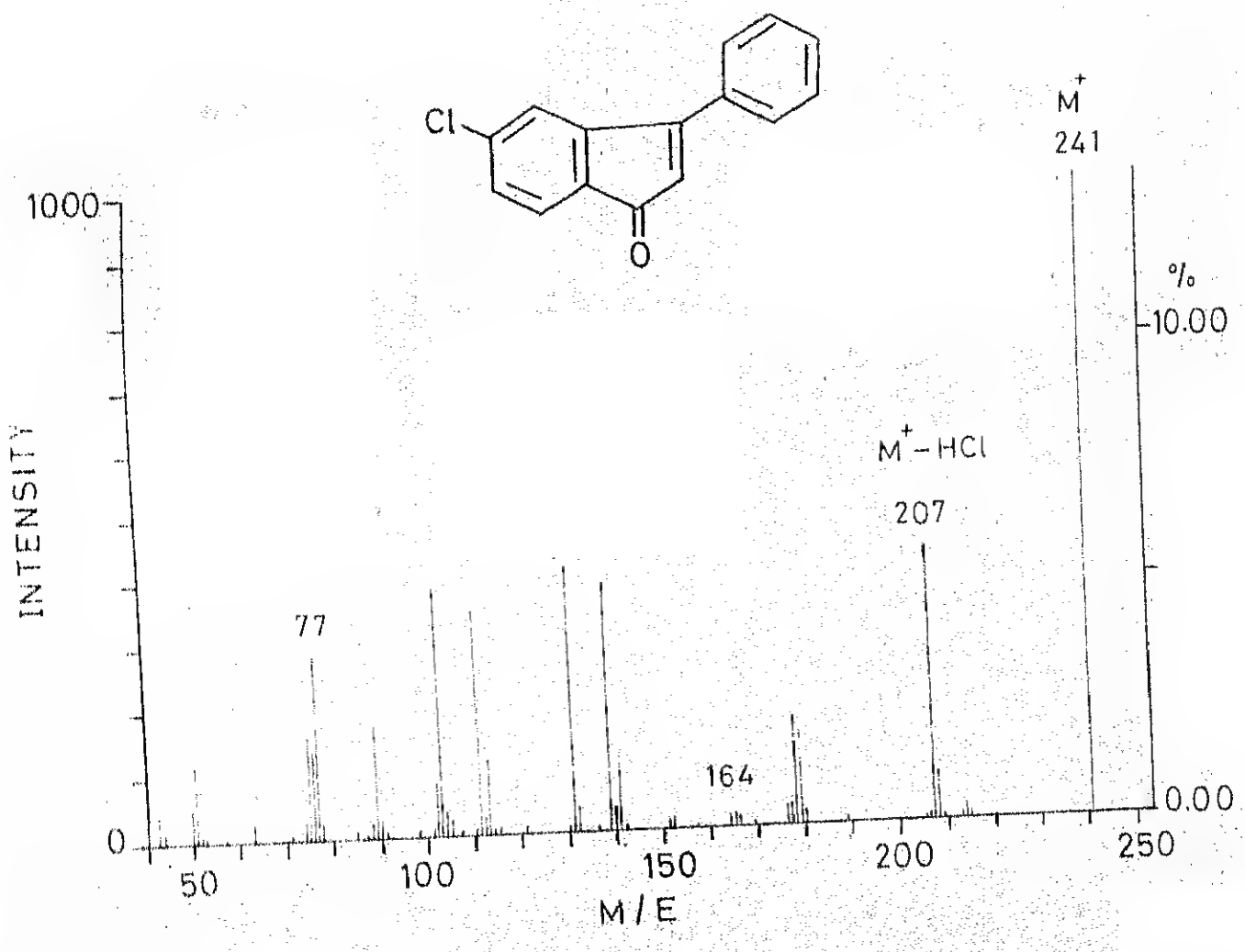


FIG. IV.1 MASS SPECTRUM OF 50a.

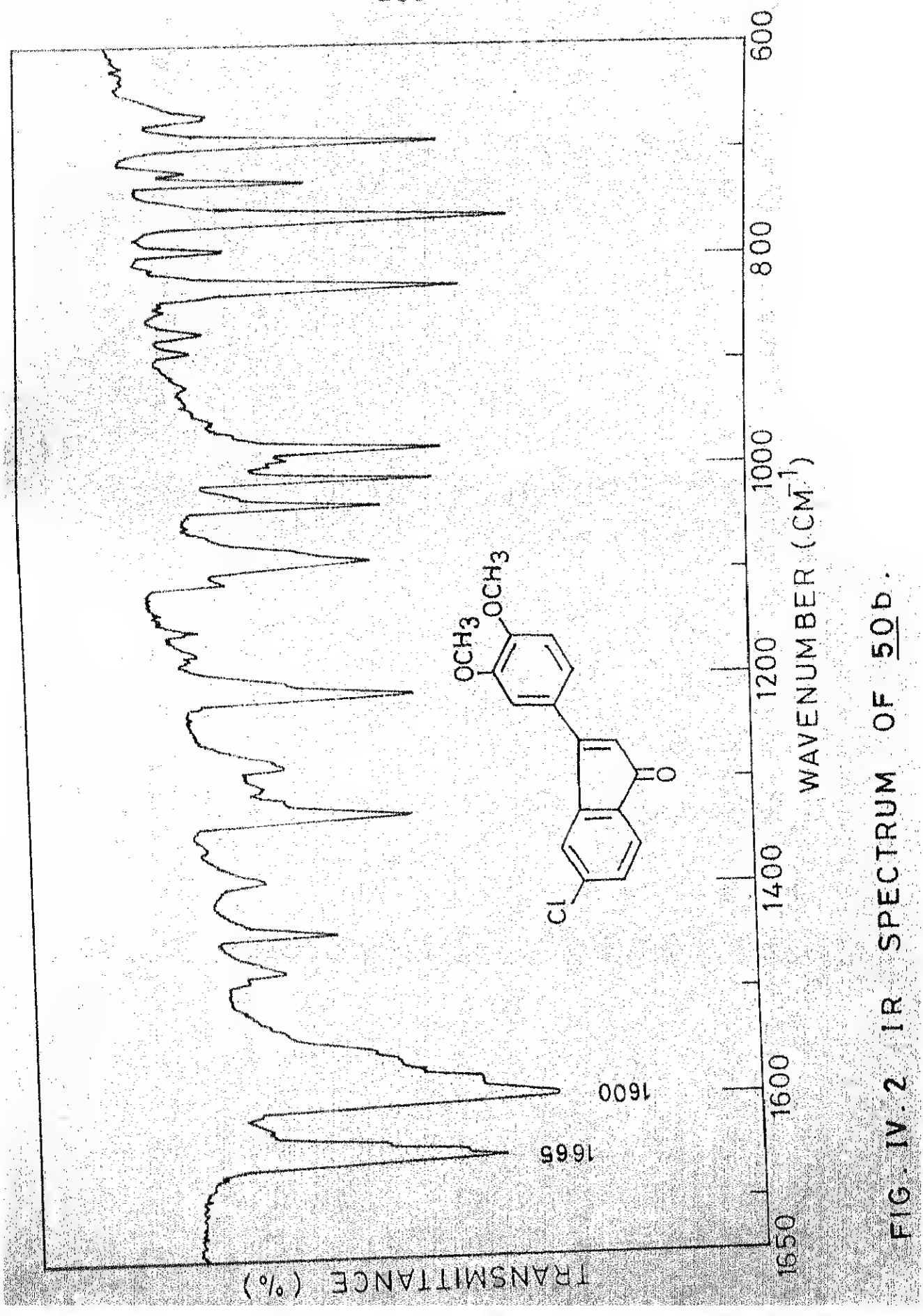


FIG. IV. 2 IR SPECTRUM OF 50b.

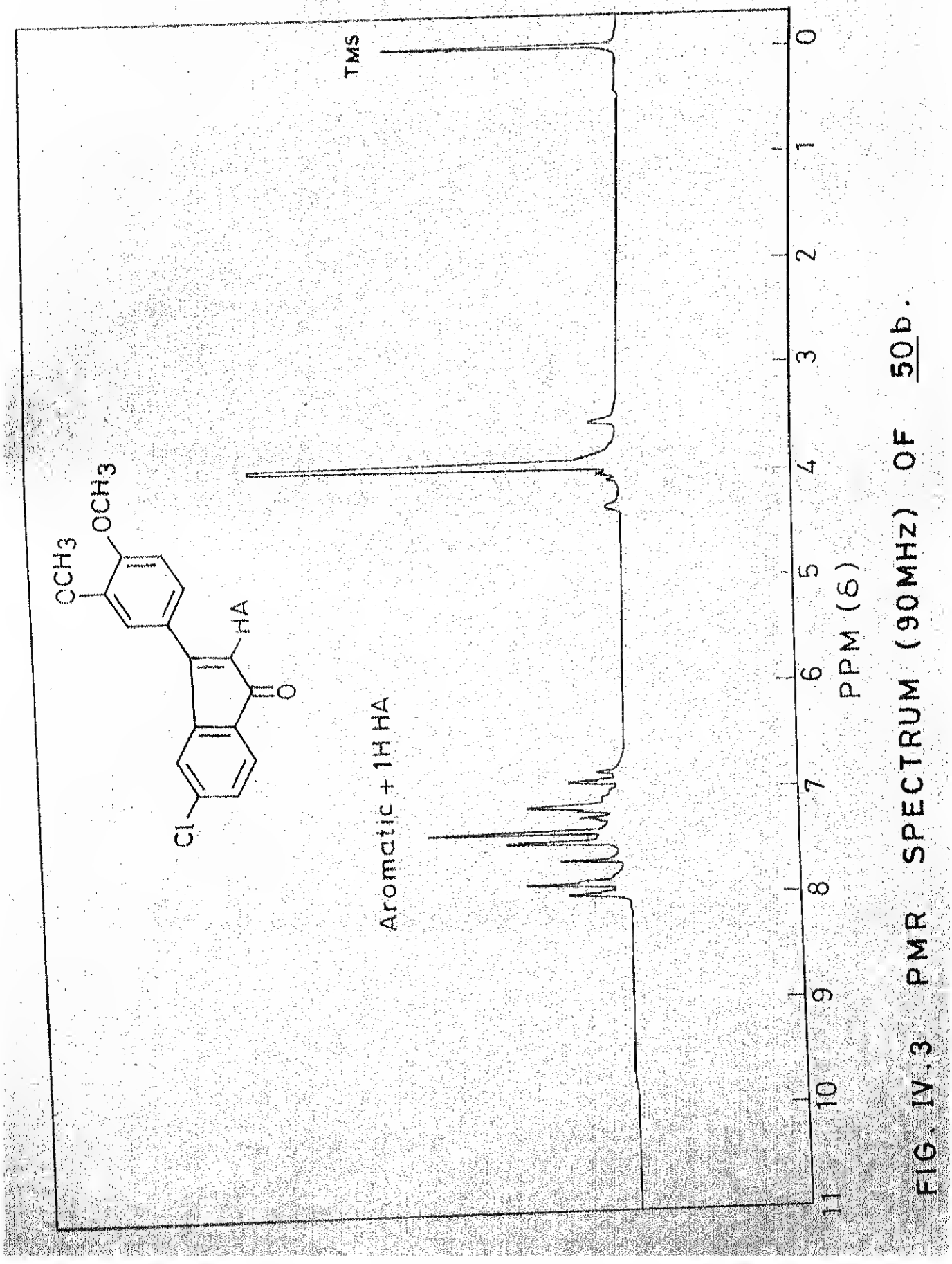


FIG. IV.3 PMR SPECTRUM (90MHz) OF 50b.

ethanol, acetic acid-O_2 failed to yield any product. Irradiation of 4'-chloro-chalcone in acetone/O_2 yielded a product which on the basis of elemental analysis corresponded to molecular formula $C_{15}H_9OCl$. It gave molecular ion peak at 241 in the mass spectrum (Fig. IV.1).

It exhibited IR absorption bands at 1665($\nu_{C=O}$), 1600, 1330, 1215, 1090, 980, 830, 760, 690. It gave PMR signals at δ 7.2-8.1 (m, 8H, aromatic +1H,CH, olefinic). It was identified as indenone derivative 50a.

Irradiation of 4'-chloro-3,4-dimethoxy-chalcone in acetone/O_2, gave rise to a product which on the basis of elemental analysis corresponded to the molecular formula $C_{17}H_{13}ClO_3$ (Fig. IV.4). It gave molecular ion peak at 301 in the mass spectrum. It exhibited IR absorption maxima at 1665($\nu_{C=O}$), 1600, 1330, 1210, 830, 750, 830,770 cm^{-1} (Fig. IV.2). It gave PMR signals at δ 6.9-8.15(m, 6H, aromatic + 1HCH, olefinic), 3.9(s,6H, OCH_3) (Fig. IV.3). It was identified at indenone derivative 50b.

Irradiation of 4'-chloro-chalcone in benzene/O_2 afforded a product which on the basis of elemental analysis corresponded to molecular formula $C_{15}H_9ClO_2$. It gave molecular ion peak at 256 in the mass spectrum. It displayed IR absorption bands at 1675($\nu_{C=O}$), 1600, 1350, 1230, 1170,cm^{-1}. It gave PMR signals at δ 6.25-7.1 (m, 8H, aromatic + 1HCH, olefinic). It was identified as 53a (Fig. IV.5).

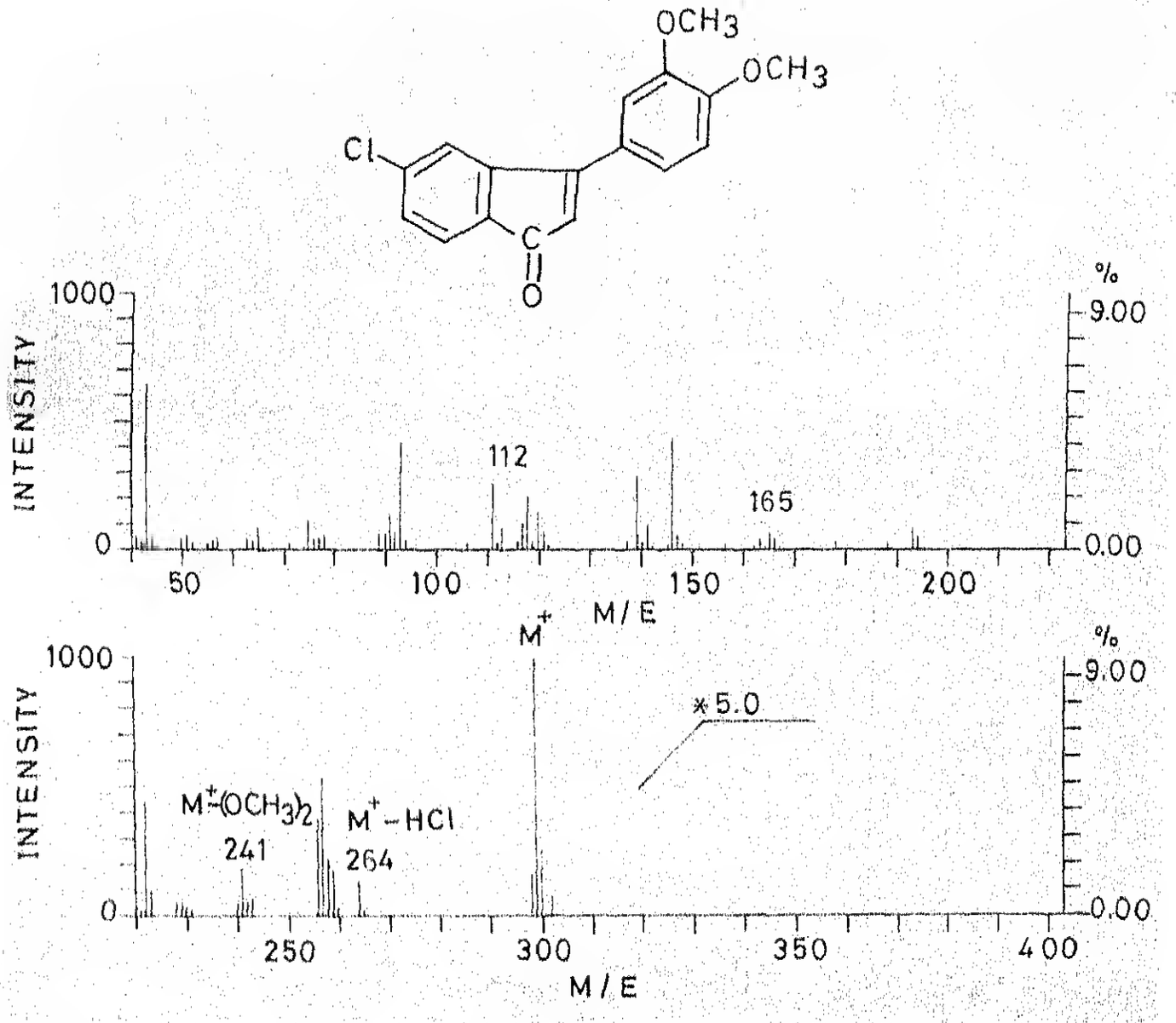


FIG. IV . 4 MASS SPECTRUM OF 50b .

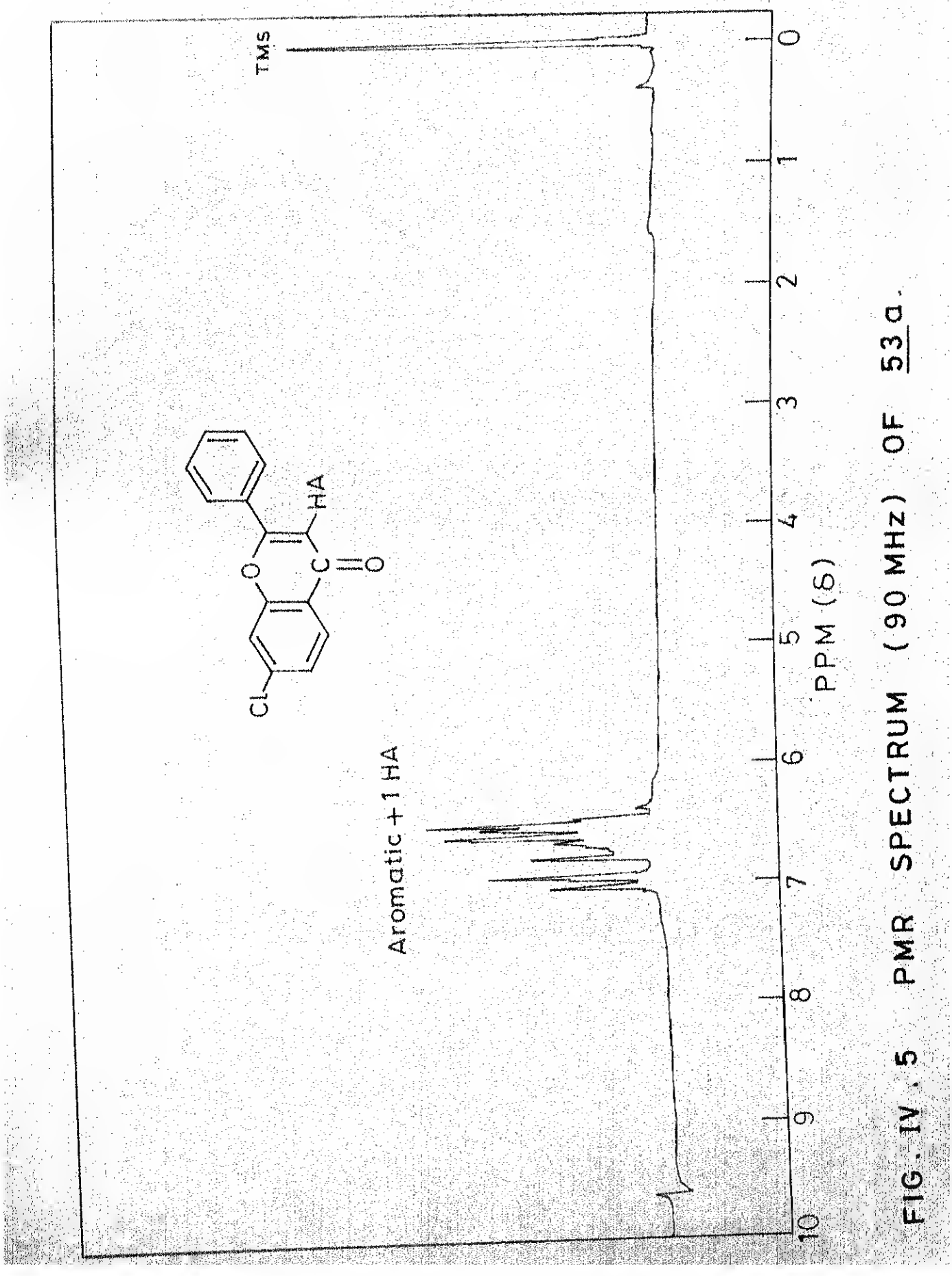


FIG. IV. 5 PMR SPECTRUM (90 MHz) OF 53a.

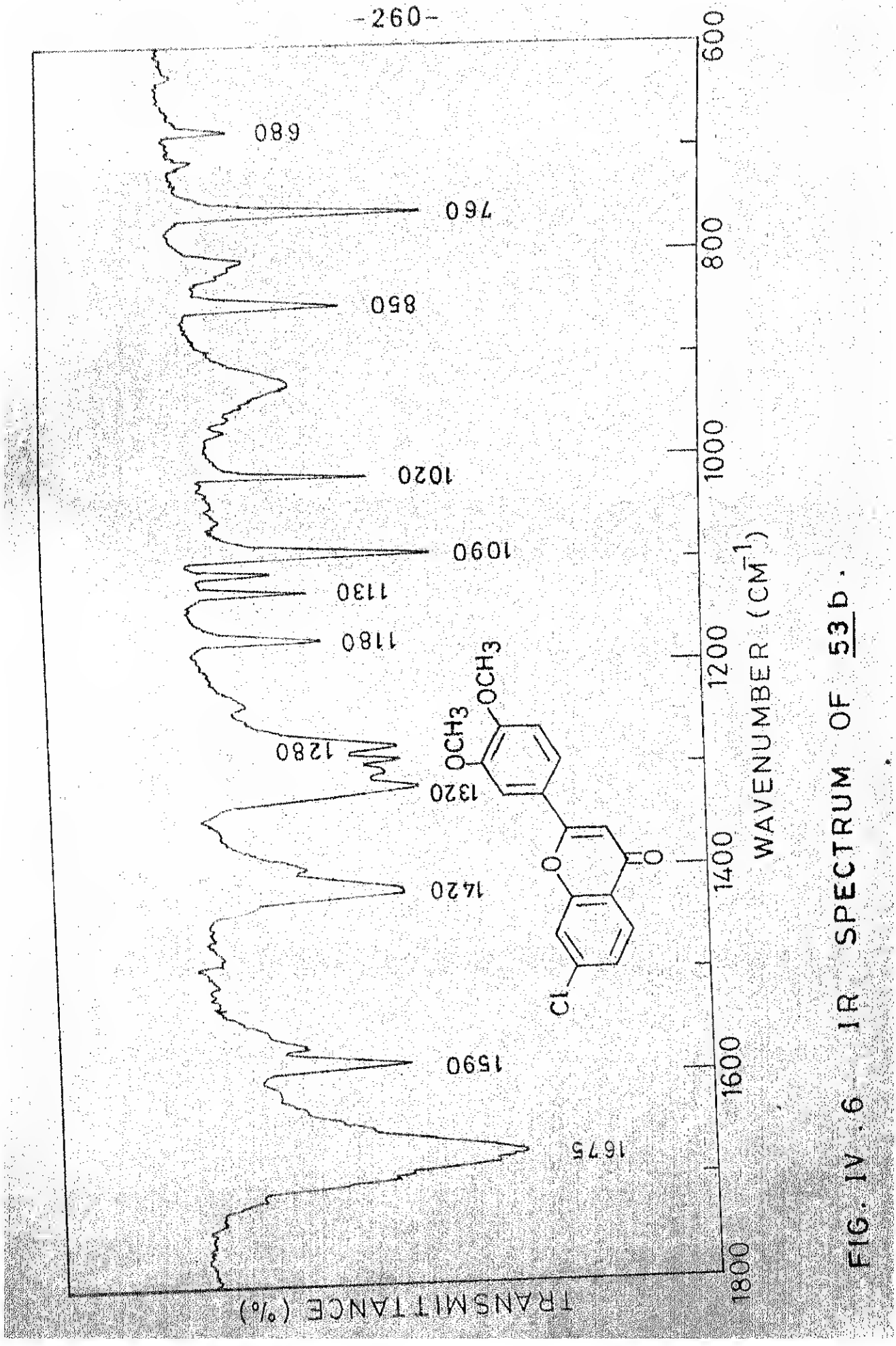
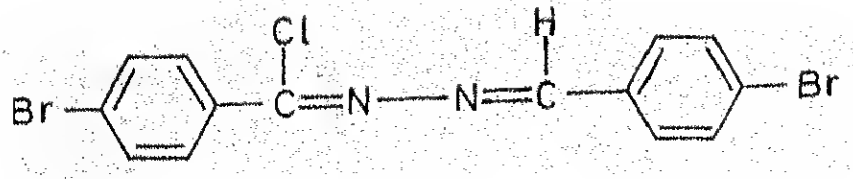


FIG. IV. 6 IR SPECTRUM OF 53b.



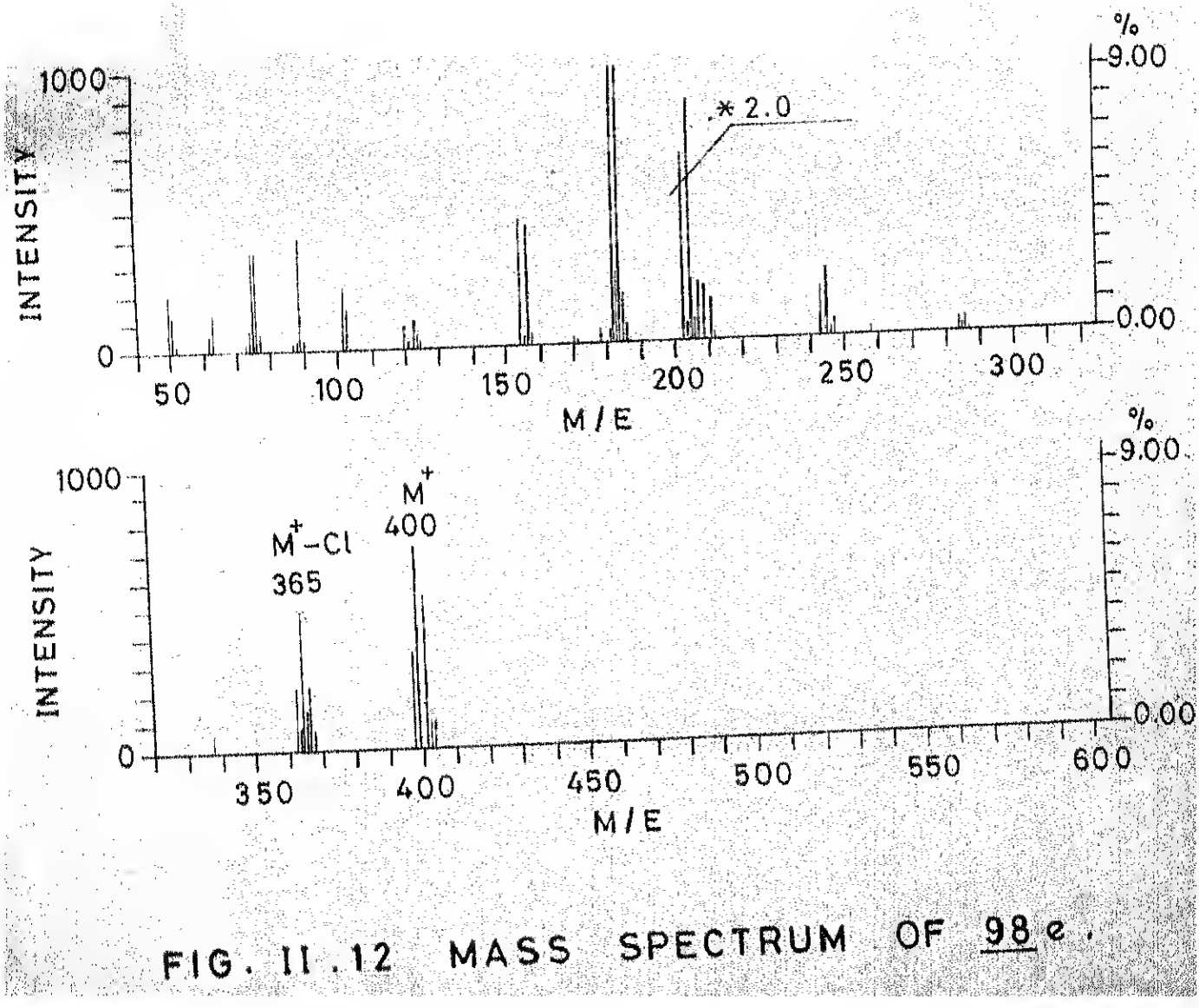


FIG. II.12 MASS SPECTRUM OF 98e.

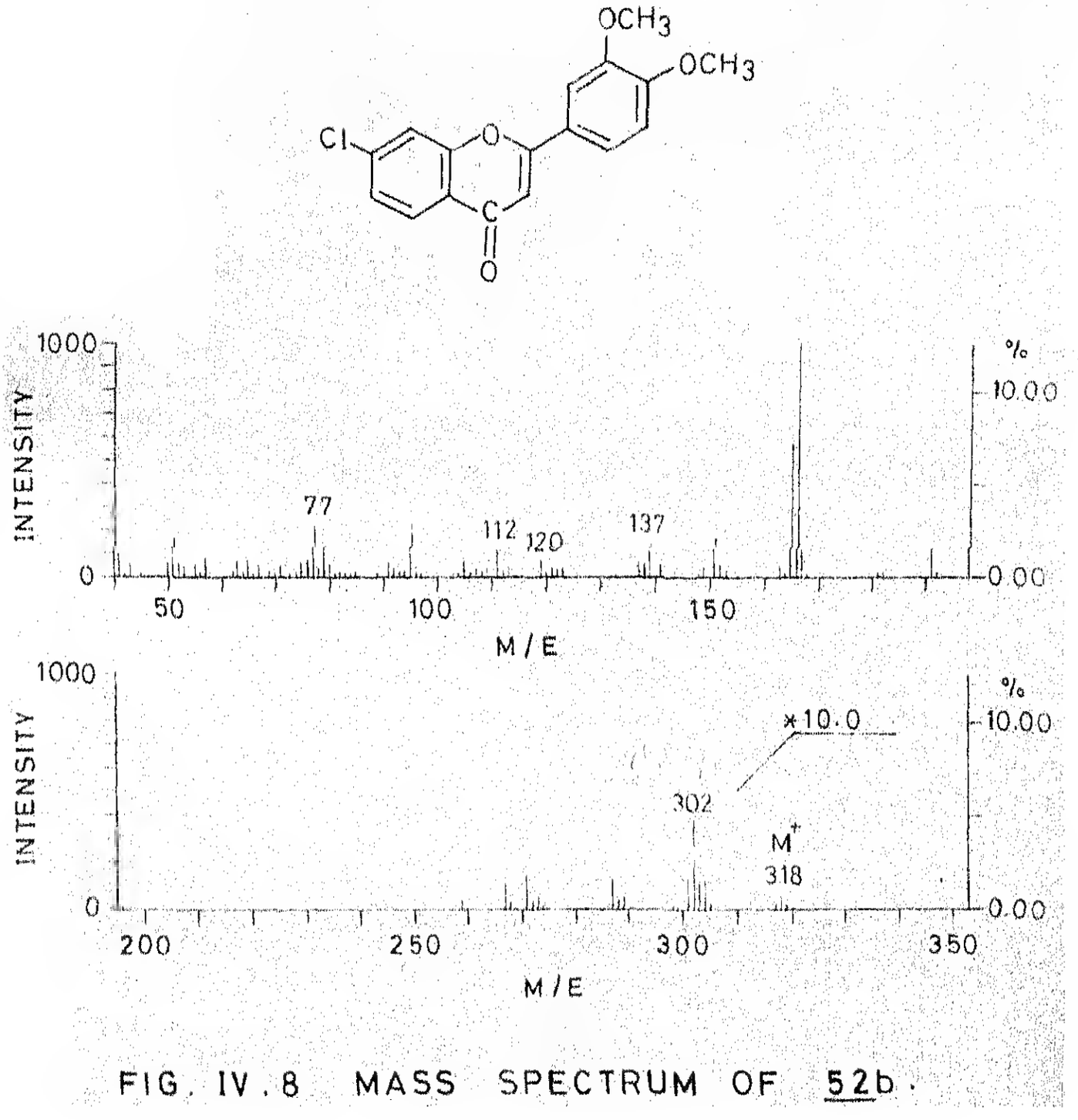


FIG. IV.8 MASS SPECTRUM OF 52b.

Irradiation of 4'-chloro-3,4-dimethoxy-chalcone in benzene/O_2 gave rise to a product which on the basis of elemental analysis corresponded to molecular formula $C_{17}H_{13}ClO_4$ (Fig. IV.8). It gave molecular ion peak at 317, in the mass spectrum. It displayed IR absorption maxima at 1675($\nu_{C=O}$), 1590, 1320, 1420, 1130 cm^{-1} (Fig. IV.6). It gave PMR signals at δ 6.2-7.2 (m, 6H, aromatic +1H, CH, olefinic), 3.8(s, 6H, OCH_3) (Fig.IV.7). It was identified as flavanone derivative 53b.

Irradiation of 4'-chloro-chalcone (as well as 3,4-dimethoxy-4'-chloro-chalcone) in methanol-O_2 yielded a product 59c which on the basis of elemental analysis corresponded to molecular formula $C_7H_5ClO_2$. It gave molecular ion peak at 157 in the mass spectrum. It was found identical in all respects (Co-TLC, m.p. and physical data) with a genuine sample of p-chlorobenzoic acid.

IV.4 EXPERIMENTAL

All the melting points are uncorrected and were taken on a Fisher-Johns melting point apparatus. The specification of the IR, PMR, and Mass spectrometers are the same as described earlier (vide Chapter-I).

Starting materials

4'-chloro-chalcone, 3,4-dimethoxy-4'-chloro-chalcone, 4'-chloro-4-acetamido-chalcone, were prepared according to the literature procedure.[31] Solvents such as benzene, methanol, acetone,

ethanol, acetic acid were purified by standard procedures. Petroleum ether used was the fraction b.p. 60-80°. All the irradiation experiments were carried out in Srinivasan Griffin Rayonet Photochemical reactor, equipped with 2537Å light source.

Preparation of indenone derivative 50a

A solution of 4'-chlorochalcone (0.01 mol) in acetone (100 ml) was irradiated for 46 hr, in presence of molecular oxygen using Srinivasan Griffin Rayonet Photochemical reactor. The experiment was repeated few times, to photolyse in all 1.2g of chalcone. Removal of the solvent under vacuum gave a residual solid which was chromatographed over silica gel. Elution with petroleum ether-benzene (4:1) afforded 25% of the unchanged starting material.

Subsquent elution of the column with petroleum ether-benzene (1:1) yielded, after recrystallization from benzene, the pure indenone derivative, 50a.

Yield: 0.602g, (50%), 115°.

Anal for $C_{15}H_9ClO$: Calcd, C, 74.68; H, 3.73%
Found, C, 73.61; H, 4.58%

IR Spectrum(KBr), ν_{max}: 1665($\nu_{C=O}$), 1600, 1330, 1215, 1090, 980, 830, 760, 690 cm^{-1}.

PMR Spectrum($CDCl_3$), δ ppm: 7.2-8.1(m, 8H, aromatic + 1H, CH, olefinic).

Mass spectrum, m/e: 241(M^+).

Preparation of indenone derivative 50b

A solution of 3,4-dimethoxy-4'-chlorochalcone in acetone (100 ml) was irradiated for 44 hr using a Srinivasan Griffin Photochemical reactor, equipped with a 2537Å light source. The photolysis was repeated several times to photolyse in all 1.5g of the chalcone. The solvent was removed under reduced pressure and the residue obtained was chromatographed over silica gel. Elution with petroleum ether-benzene (3:1) afforded 50b (after recrystallization from benzene).

Further elution of the column with different solvents gave a complex mixture of products, from which no definite product(s) could be isolated.

Yield: 0.785g, (52%), m.p. 140-141°.

Anal for $C_{17}H_{15}ClO_3$: Calcd, C, 67.54; H, 4.96%
Found, C, 68.56; H, 5.61%

IR Spectrum(KBr), ν_{max}: 1660($\nu_{C=O}$), 1600, 1330, 1210, 830, 750, 770 cm^{-1},

PMR Spectrum($CDCl_3$), δ ppm: 6.9-8.15(m, 6H, aromatic + 1H, CH), 3.9 (s, 6H, OCH_3).

Mass spectrum, m/e: 301(M^+).

Preparation of flavanone derivative 53a

A solution of 4'-chloro-chalcone (0.1 mol) in benzene (100 ml) was irradiated using molecular O_2 for 44 hr, in Srinivasan Griffin Rayonet Photochemical reactor, the experiment was repeated a few times to photolyse in all 1.2g of chalcone. Removal of the solvent under diminished pressure gave a residue which was chromatographed over silica gel. Elution with mixture of (4:1) of petroleum ether and benzene gave 12% of the unchanged starting material.

Subsequent elution of the column with a mixture of (1:1) mixture of petroleum ether and benzene gave 53a, it was recrystallized from benzene.

Yield: 0.665g, (52%), m.p. 118-119°.

Anal for $C_{15}H_9O_2Cl$: Calcd, C, 67.77; H, 4.31%

Found, C, 67.02; H, 4.21%

IR Spectrum(KBr), ν_{max}: 1675($\nu_{C=O}$), 1600, 1390, 1230, 1170, 890, 690 cm^{-1}.

PMR Spectrum($CDCl_3$), δ ppm: 6.25-7.1 (m, 8H, aromatic + 1HCH, olefinic).

Mass spectrum, m/e: 256(M^+).

Preparation of flavanone derivative 53b

A solution of 4'-chloro-chalcone (0.01 mol) in benzene (100 ml) was irradiated for 44 hr using Srinivasan Griffin Rayonet Photochemical reactor. The experiment was repeated a few times, to photolyse in all 1.5g of chalcone. Removal of the solvent under vacuum gave a residual solid which was chromatographed over silica gel. Elution with petroleum ether-benzene (4:1) afforded 15% of the unchanged starting material.

Subsequent elution of the column with a mixture of (1:1), petroleum ether and benzene gave 53b, it was recrystallized from benzene.

Yield: 0.808g, (51%), m.p. 125-126°.

Anal for $C_{17}H_{13}O_3Cl$: Calcd, C, 67.77; H, 4.31%
Found, C, 67.60; H, 4.21%

IR Spectrum(KBr), ν_{max}: 1675($\nu_{C=O}$), 1590, 1320, 1020, 850, 760, 680 cm^{-1}.

PMR Spectrum($CDCl_3$), δ ppm: 6.2-7.2 (m, 6H, aromatic +1H/CH), 3.7 (d, 6H, OCH_3).

Mass spectrum, m/e: 317(M^+), 301.

Preparation of p-chloro-benzoic acid 59c

To a solution of 4'-chloro-chalcone in methanol (100 ml)/O_2

was irradiated for 42 hr using Srinivasan Rayonet Photochemical reactor. The experiment was repeated a few times to photolyse in all, 1.2g of the chalcone. Removal of the solvent in vacuo, gave a solid, which was chromatographed over silica gel. Elution with a petroleum ether-benzene (4:1) gave 10% unchanged starting material. Subsequent elution of the column with benzene-ethyl acetate (1:4) furnished 59c. It was recrystallized from ethanol to give p-chlorobenzoic acid. Yield: 0.390g, (50%), m.p. 233-234°.

It was found identical in all respects (Co-TLC, m.p. and physical data) with a genuine sample of p-chloro-benzoic acid.

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VITAE

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